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(54) Title: **SUBSTITUTED SULFONAMIDE COMPOUNDS, PROCESS FOR THEIR USE AS MEDICAMENT FOR THE  
TREATMENT OF CNS DISORDERS, OBESITY AND TYPE II DIABETES**

(57) Abstract: **The present invention relates to substituted sulfonamide compounds of the general formula (I), wherein P is sul-  
fonamide or amide-substituted sulfonic acid, which compounds are potentially useful for the prophylaxis and treatment of medical  
conditions relating to obesity, type II diabetes and/or disorders of the central nervous system.**

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**SUBSTITUTED SULFONAMIDE COMPOUNDS , PROCESS FOR  
THEIR PREPARATION, AND THEIR USE AS, MEDICAMENT FOR THE  
TREATMENT OF CNS DISORDERS, OBESITY AND TYPE II  
DIABETES.**

**TECHNICAL FIELD**

5       The present invention relates to substituted sulfonamide compounds, to  
pharmaceutical compositions comprising these compounds, and to the use of the compounds  
for the prophylaxis and treatment of medical conditions relating to obesity, type II diabetes,  
and CNS disorders.

10       **BACKGROUND ART**

Obesity is a condition characterized by an increase in body fat content resulting in  
excess body weight above accepted norms. Obesity is the most important nutritional disorder  
in the western world and represents a major health problem in all industrialized countries.

15       This disorder leads to increased mortality due to increased incidences of diseases such as  
cardiovascular disease, digestive disease, respiratory disease, cancer and type II diabetes.  
Searching for compounds, which reduce body weight has been going on for many decades.  
One line of research has been activation of serotonergic systems, either by direct activation  
of serotonin receptor subtypes or by inhibiting serotonin reuptake. The exact receptor  
20       subtype profile required is however not known.

Serotonin (5-hydroxytryptamine or 5-HT), a key transmitter of the peripheral and  
central nervous system, modulates a wide range of physiological and pathological functions,  
including anxiety, sleep regulation, aggression, feeding and depression. Multiple serotonin  
25       receptor subtypes have been identified and cloned. One of these, the 5-HT<sub>6</sub> receptor, was  
cloned by several groups in 1993 (Ruat, M. et al. (1993) Biochem. Biophys. Res.  
Commun.193: 268-276; Sebben, M. et al. (1994) NeuroReport 5: 2553-2557). This receptor  
is positively coupled to adenylyl cyclase and displays affinity for antidepressants such as  
clozapine. Recently, the effect of 5-HT<sub>6</sub> antagonist and 5-HT<sub>6</sub> antisense oligonucleotides to

reduce food intake in rats has been reported (Bentley, J.C. et al. (1999) Br J Pharmac. Suppl. 126, P66; Bentley, J.C. et al. (1997) J. Psychopharmacol. Suppl. A64, 255).

Compounds with enhanced affinity and selectivity for the 5-HT<sub>6</sub> receptor have been  
5 identified, e.g. in WO 00/34242 and by Isaac, M. et al. (2000) *6-Bicyclopiperazinyl-1-arylsulfonylindoles and 6-Bicyclopiperidinyl-1-arylsulfonylindoles derivatives as novel, potent and selective 5-HT<sub>6</sub> receptor antagonists*. Bioorganic & Medicinal Chemistry Letters 10: 1719-1721 (2000).

10

## INFORMATION DISCLOSURE

J. Med. Chem. 1970, 13(4), 592-598 describes N-(4-{[2-(diethylamino)ethyl]amino}-1-naphthyl)amides; N-{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}amides and related amides and urea derivatives as schistosomicides.

15 WO 99/42465 discloses sulfonamides derivatives that bind to the 5-HT<sub>6</sub> receptor and that can be used for the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, cognitive disorders, ADHD, anorexia and bulimia schizophrenia, drug abuse.

WO 01/32646 A1 discloses compounds that binds to the 5-HT<sub>6</sub> receptor and that are used for  
20 the treatment of CNS disorders and which inter alia may be used for the treatment of eating disorders.

WO 99/37623 A2 discloses compounds that binds to the 5-HT<sub>6</sub> receptor and that are used for the treatment of CNS disorders and which inter alia may be used for the treatment of eating disorders.

25 WO 99/42465 A3 discloses compounds that binds to the 5-HT<sub>6</sub> receptor and that are used for the treatment of CNS disorders and which inter alia may be used for the treatment of eating disorders.

EP 0 815 861 A1 discloses compounds that binds to the 5-HT<sub>6</sub> receptor and that are used for the treatment of CNS disorders.

WO 99/02502 A2 discloses compounds that binds to the 5-HT<sub>6</sub> receptor and that are used for the treatment of CNS disorders and which inter alia may be used for the treatment of eating disorders.

WO 98/27081 A1 discloses compounds that binds to the 5-HT<sub>6</sub> receptor and that are used for the treatment of CNS disorders and which inter alia may be used for the treatment of eating disorders.

### DISCLOSURE OF THE INVENTION

It has surprisingly been found that the compounds of formula (I) show affinity for the 5-HT<sub>6</sub> receptor as antagonists at low nanomolar range. Compounds according to the invention and their pharmaceutically acceptable salts have 5-HT<sub>6</sub> receptor antagonist activity and are believed to be of potential use in the treatment or prophylaxis of obesity and type II diabetes, as well as in the treatment or prophylaxis of disorders of the central nervous system such as anxiety, depression, panic attacks, memory disorders, sleep disorders, migraine, anorexia, bulimia, binge disorders, obsessive compulsive disorders, psychoses, Alzheimer's disease, Parkinson's disease, Huntington's chorea and/or schizophrenia, Attention Deficit Hyperactive Disorders (ADHD), drug abuse.

#### *Definitions*

Unless otherwise stated or indicated, the term "C<sub>1-6</sub> alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said lower alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

Unless otherwise stated or indicated, the term "C<sub>1-6</sub> alkoxy" denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms. Examples of said lower alkoxy include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy and straight- and branched-chain pentoxy and hexoxy.



Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine, bromine or iodine.

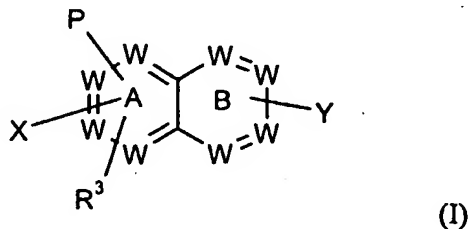
The term "C<sub>3-7</sub> cycloalkyl" denotes a cyclic alkyl group having a ring size from C<sub>3</sub> to C<sub>7</sub>. Examples of said cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclohexyl and cycloheptyl.

The term "heterocyclic" refers to a hydrocarbon ring system containing 4 to 8 ring members that have at least one heteroatom (e.g., S, N, or O) as part of the ring. It includes saturated, unsaturated, aromatic, and nonaromatic heterocycles. Suitable heterocyclic groups include thienyl, furyl, pyridyl, pyrrolidinyl, imidazolyl, pyrazolyl, piperidyl, azepinyl, morpholinyl, pyranal, dioxanyl, pyridazinyl, pyrimidinyl, and piperazinyl groups

The term "heteroaryl" refers to a hydrocarbon ring system having at least one aromatic ring which contains at least one heteroatom such as O, N, or S. Examples of heteroaryl groups include furyl, pyrrolyl, thienyl, oxazolyl, imidazolyl, thiazolyl, pyridinyl, pyrimidinyl, quinazolinyl, and indolyl groups.

### Compounds of Formula I

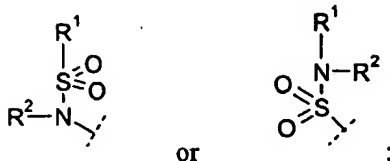
In a first aspect, the present invention provides a compound having the general formula I:



or a pharmaceutically acceptable salt thereof, wherein:

W is N or  $-(CH)-$ , provided that not more than three groups W are N;

P is



5

with the proviso that P and  $R^3$  can only be in *meta* or *para* position to each other;

$R^1$  is

- (a)  $C_{1-6}$  alkyl,
- 10 (b)  $C_{1-6}$  alkoxyalkyl,
- (c) straight or branched  $C_{1-6}$  hydroxyalkyl,
- (d) straight or branched  $C_{1-6}$  alkylhalides; or
- (e) a group Ar;

15 Ar is

- (a) phenyl,
- (b) 1-naphthyl,
- (c) 2-naphthyl,
- (d) benzyl,
- 20 (e) cinnamoyl,
- (f) a 5 to 7-membered, optionally aromatic, partially saturated or completely saturated, heterocyclic ring containing 1 to 4 heteroatoms, selected from oxygen, nitrogen and sulfur, or
- (g) a bicyclic ring system comprising at least one heterocyclic ring according to (f).

25 wherein the group Ar is substituted in one or more positions with

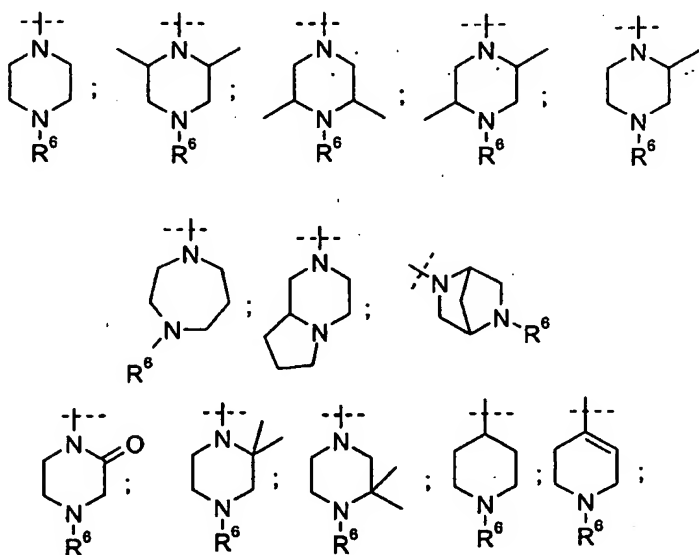
- (a) H, X or Y, or

(b) a 5 to 7-membered, optionally aromatic, partially saturated or completely saturated, mono- or bi-cyclic heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;

5  $R^2$  is

- (a) H,
- (b)  $C_{1-6}$  alkyl,
- (c)  $C_{1-6}$  alkoxyalkyl,
- (d) straight or branched  $C_{1-6}$  hydroxyalkyl, or
- 10 (e) straight or branched  $C_{1-6}$  alkylhalides;

$R^3$  is a group



15

X and Y are independently

- (a) H,
- (b) halogen,
- (c)  $C_{1-6}$  alkyl,

20 (d)  $CF_3$ ,

- (e) hydroxy,
- (f) C<sub>1-6</sub> alkoxy,
- (g) C<sub>1-4</sub> alkenyl;
- (h) phenyl;
- 5 (i) phenoxy,
- (j) benzyloxy,
- (k) benzoyl,
- (l) -OCF<sub>3</sub>,
- (m) -CN,
- 10 (n) straight or branched C<sub>1-6</sub> hydroxyalkyl,
- (o) straight or branched C<sub>1-6</sub> alkylhalides,
- (p) -NH<sub>2</sub>,
- (q) -NHR<sup>4</sup>,
- (r) -NR<sup>4</sup>R<sup>5</sup>,
- 15 (s) -NO<sub>2</sub>,
- (t) -CON R<sup>4</sup>R<sup>5</sup>,
- (u) -NHSO<sub>2</sub> R<sup>4</sup>,
- (v) -NR<sup>6</sup>COR<sup>5</sup>,
- (x) -SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>,
- 20 (z) -C(=O) R<sup>4</sup>,
- (aa) -CO<sub>2</sub> R<sup>4</sup>, or
- (ab) -S(O)<sub>n</sub> R<sup>4</sup>; wherein n is 0, 1, 2 or 3,
- (ac) -S-(C<sub>1-6</sub>)alkyl
- (ad) -SCF<sub>3</sub>

25

R<sup>4</sup> and R<sup>5</sup> are independently

- (a) H,
- (b) C<sub>1-6</sub> alkyl,
- (c) C<sub>3-7</sub> cycloalkyl, or
- 30 (d) Ar, as defined above for R<sup>1</sup>;

alternatively, R<sup>4</sup> and R<sup>5</sup> are linked to form a group (CH<sub>2</sub>)<sub>2</sub>O, (CH<sub>2</sub>)<sub>4</sub>O or (CH<sub>2</sub>)<sub>3-5</sub>; and

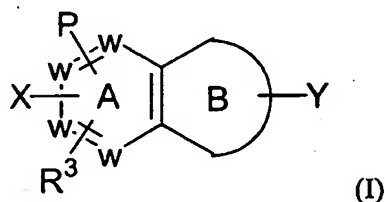
$R^6$  is

(a) H, or

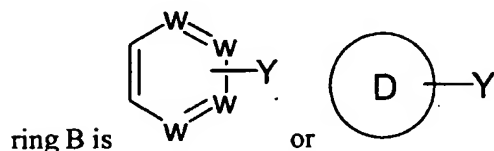
(b)  $C_{1-6}$  alkyl.

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In one aspect, this invention features a compound of the formula (I):



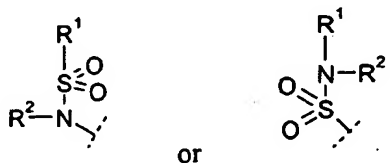
10 or a pharmaceutically acceptable salt thereof, wherein:



15

W is N or  $-(CH)-$ , provided that not more than three groups W are N in both rings A and B together;

P is



20

P and  $R^3$  are bound to the same ring and are disposed in the meta- or para-positions relative to each other;

R<sup>1</sup> is

- (a) C<sub>1-6</sub> alkyl,
- (b) C<sub>1-6</sub> alkoxyalkyl,
- 5 (c) straight or branched C<sub>1-6</sub> hydroxyalkyl,
- (d) straight or branched C<sub>1-6</sub> alkylhalides; or
- (e) a group Ar;

Ar is

- 10 (a) phenyl,
- (b) 1-naphthyl,
- (c) 2-naphthyl,
- (d) benzyl,
- (e) cinnamoyl,
- 15 (f) a 5 to 7-membered, optionally aromatic, partially saturated or completely saturated, heterocyclic ring containing 1 to 4 heteroatoms, selected from oxygen, nitrogen and sulfur, or
- (g) a bicyclic ring system comprising at least one heterocyclic ring according to (f).

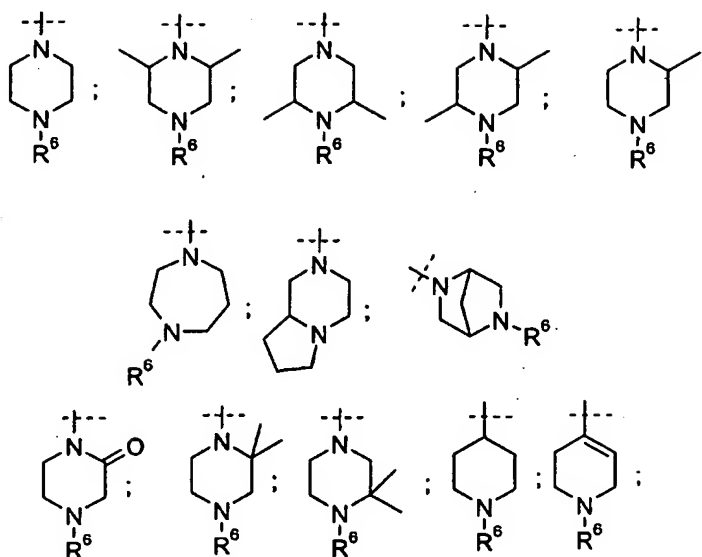
wherein the group Ar is substituted in one or more positions with

- 20 (a) H, X or Y, or
- (b) a 5 to 7-membered, optionally aromatic, partially saturated or completely saturated, heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;

25 R<sup>2</sup> is

- (a) H,
  - (b) C<sub>1-6</sub> alkyl,
  - (c) C<sub>1-6</sub> alkoxy,
  - (d) straight or branched C<sub>1-6</sub> hydroxyalkyl, or
  - 30 (e) straight or branched C<sub>1-6</sub> alkylhalides;
- or R<sup>1</sup> and R<sup>2</sup> are linked to form a group (CH<sub>2</sub>)<sub>4</sub>O;

One of  $R^3$  is a group



5

X and Y are independently

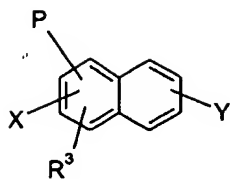
- (a) H,
- (b) halogen,
- (c)  $C_{1-6}$  alkyl,
- 10 (d)  $-CF_3$ ,
- (e) hydroxy,
- (f)  $C_{1-6}$  alkoxy,
- (g)  $C_{1-4}$  alkenyl;
- (h) phenyl;
- 15 (i) phenoxy,
- (j) benzyloxy,
- (k) benzoyl,
- (l)  $-OCF_3$ ,
- (m)  $-CN$ ,
- 20 (n) straight or branched  $C_{1-6}$  hydroxyalkyl,

- (o) straight or branched C<sub>1-6</sub> alkylhalides,
- (p) -NH<sub>2</sub>,
- (q) -NHR<sup>4</sup>,
- (r) -NR<sup>4</sup>R<sup>5</sup>,
- 5 (s) -NO<sub>2</sub>,
- (t) -CONR<sup>4</sup>R<sup>5</sup>,
- (u) -NHSO<sub>2</sub>R<sup>4</sup>,
- (v) -NR<sup>4</sup>COR<sup>5</sup>,
- (x) -SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>,
- 10 (z) -C(=O)R<sup>4</sup>,
- (aa) -CO<sub>2</sub>R<sup>4</sup>, or
- (ab) -S(O)<sub>n</sub>R<sup>4</sup>; wherein n is 0, 1, 2 or 3;
- (ac) -S-(C<sub>1-6</sub>)alkyl
- (ad) -SCF<sub>3</sub>
- 15 R<sup>4</sup> and R<sup>5</sup> are independently
- (a) H,
- (b) C<sub>1-6</sub> alkyl,
- (c) C<sub>3-7</sub> cycloalkyl, or
- 20 (d) Ar, as defined above for R<sup>1</sup>;
- alternatively, R<sup>4</sup> and R<sup>5</sup> are linked to form a group (CH<sub>2</sub>)<sub>2</sub>O, (CH<sub>2</sub>)<sub>4</sub>O or (CH<sub>2</sub>)<sub>3-5</sub>; and
- R<sup>6</sup> is
- (a) H, or
- 25 (b) straight or branched C<sub>1-6</sub> alkyl.

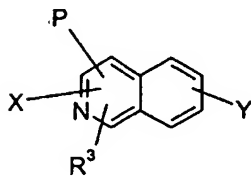
In preferred forms, the invention provides naphthalene compounds of the formula (II), isoquinoline compounds of the formula (III), quinoline compounds of the formula (IV), 1,7-naphthyridine compounds of the formula (V), and benzofuran, benzothiophene, or indole compounds of the formula (VI):

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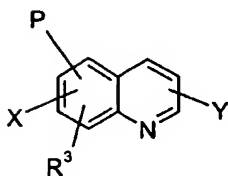




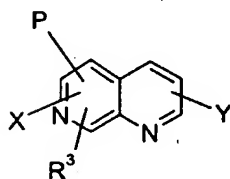
(II)



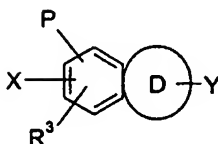
(III)



(IV)



(V)



(VI)

- 10 wherein  $R^3$ , P, X and Y are as defined for formula (I); and wherein D in formula (VI) is a five-membered heterocyclic or heteroaryl ring, said ring comprising one or two atoms selected from the group consisting of nitrogen, sulfur and oxygen, with the proviso that when D contains an oxygen atom, D is heteroaryl. The group Y can be attached to any unsubstituted carbon atom in D. When the heteroaryl ring comprises one or two nitrogen
- 15 atoms, a group  $R^6$  could be attached at the secondary nitrogen.

Preferred compounds of the general formulas (I), (II), (III), and (IV), (V), (VI) are those wherein:

R<sup>1</sup> is

- 5 (a) C<sub>1-6</sub> alkyl, or  
(e) a group Ar;

Ar is

- (a) phenyl,  
10 (b) 1-naphthyl,  
(c) 2-naphthyl, or  
(f) a 5 to 7-membered, partially or completely saturated, mono- or bi-cyclic heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur;

- 15 wherein the group Ar is substituted in one or more positions with X or Y; wherein X or Y is

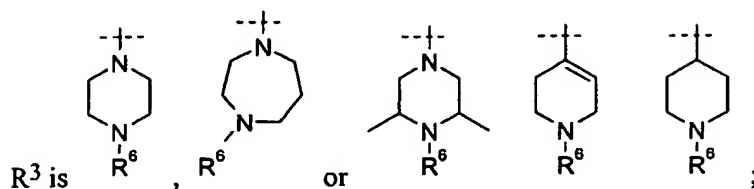
- (a) H,  
(b) halogen,  
(c) C<sub>1-6</sub> alkyl,  
(d) -CF<sub>3</sub>,  
20 (f) C<sub>1-6</sub> alkoxy,  
(g) C<sub>1-4</sub> alkenyl;  
(l) -OCF<sub>3</sub>, or  
(m) straight or branched C<sub>1-6</sub> hydroxyalkyl  
(n) phenyloxy  
25 (o) benzyloxy  
(ab) -S(O)<sub>n</sub>R<sup>4</sup>; wherein n is 0, 1, 2 or 3,  
(ac) -S-(C<sub>1-6</sub>)alkyl  
(ad) -SCF<sub>3</sub>  
(v) -NR<sup>4</sup>COR<sup>5</sup>,  
30 (x) -SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>,  
(z) -C(=O)R<sup>4</sup>.

$R^2$  is

(a) H, or

(b)  $C_{1-3}$  alkyl, in particular methyl;

5 or  $R^1$  and  $R^2$  are linked to form a group  $(CH_2)_4O$ ;



wherein  $R^6$  is

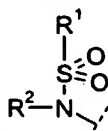
10 (a) H, or


(b)  $C_{1-6}$  alkyl, in particular methyl;

X and Y are H; and/or

15 D is furanyl.

Preferred compounds of the formula II are para-substituted naphthalene compounds



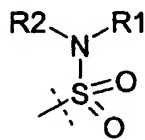
wherein P is  , wherein  $R^1$  and  $R^2$  are as defined for formula (I); and X and Y are

H, halogens, methyl, methoxy, (cf. Table I). Particularly preferred of such compounds are

20 those wherein  $R^1$  is phenyl, methylphenyl, methoxyphenyl, dimethoxyphenyl, 1-naphthyl, 2-naphthyl, fluoromethylphenyl, chlorophenyl, dichlorophenyl, fluorochlorophenyl, dichlorothiophenyl, chlorothiophenyl, trifluoromethylphenyl, or methoxymethylphenyl;  $R^2$  is H or methyl; and  $R^3$  is piperazinyl or homopiperazinyl, 3,5-dimethylpiperazine, 4-piperidine, 4-(4,3)-dihydropyridine, 4-(1,2,3,6)-tetrahydropyridine;  $R^6$  is H, methyl, ethyl, isopropyl.

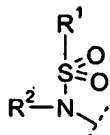
Further preferred compounds of the formula II are compounds with a group P and a group R<sup>3</sup> in para-position.

Further preferred compounds of the formula II are compounds with a group P and a



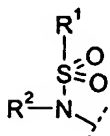
5 group R<sup>3</sup> in para-position, wherein P is , wherein R<sup>1</sup> and R<sup>2</sup> are as defined for formula (I) (cf. Table III); and X or Y are H, methyl, ethyl, isopropyl, methoxy, thiomethyl, 1-naphthyl, phenoxy, trifluoromethoxy, trifluorothienyl (cf. Table II). Particularly preferred of such compounds are those wherein R<sup>1</sup> is phenyl, 1-naphthyl, phenoxyphenyl, dimethoxyphenyl, dimethylphenyl, methylchlorophenyl, isopropylphenyl, fluorophenyl,  
10 1(2H)-3,4-dihydroquinolin, R<sup>2</sup> is H or methyl, R<sup>3</sup> is piperazinyl, and R<sup>6</sup> is H.

Preferred compounds of the formula III are isoquinoline compounds wherein P is



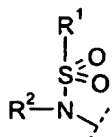
and occupies position 3 of the ring; wherein R<sup>1</sup> and R<sup>2</sup> are as defined for formula (I); and X or Y are H, methyl, bromo, methoxy, acethylamino (cf. Table IV). Particularly  
15 preferred of such compounds are those wherein R<sup>1</sup> is phenyl, bromophenyl, methylchlorophenyl, methylphenyl, methoxyphenyl, trimethylphenyl, dimethoxyphenyl, bromomethoxyphenyl; R<sup>2</sup> is H or methyl; and R<sup>3</sup> is methylpiperazinyl.

Preferred compounds of the formula IV are quinoline compounds wherein P is



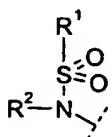
20 and occupies position 5 of the ring, wherein R<sup>1</sup> and R<sup>2</sup> are as defined for formula (I); and X, Y is H (cf. Table V). Particularly preferred of such compounds are those wherein R<sup>1</sup> is phenyl; R<sup>2</sup> is H or methyl; and R<sup>3</sup> is piperidinyl.

Preferred compounds of the formula V are 1,7-naphthyridine compounds wherein P is



and occupies position 8 of the ring, wherein R<sup>1</sup> and R<sup>2</sup> are as defined for formula (I); and X and Y are halogen, methoxy (cf. Table V). Particularly preferred of such compounds are those wherein R<sup>1</sup> is phenyl, dimethoxyphenyl, 1-naphthyl; R<sup>2</sup> is H or methyl; and R<sup>3</sup> is piperidinyl;

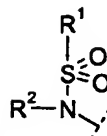
Preferred compounds of the formula VI are benzofurane compounds wherein P is



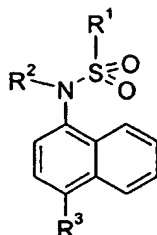
and occupies position 5 of the ring, wherein R<sup>1</sup> and R<sup>2</sup> are as defined for formula (I) and wherein D in formula (VI) is a five-membered heterocyclic or heteroaryl ring, said ring comprising one or two atoms selected from the group consisting of nitrogen, sulfur and oxygen, with the proviso that when D contains an oxygen atom, D is heteroaryl. The group Y can be attached to any unsubstituted carbon atom in D. When the heteroaryl ring comprises one or two nitrogen atoms, a group R<sup>6</sup> could be attached at the secondary nitrogen; and X and Y are halogen, methoxy (cf. Table V). Particularly preferred of such compounds are those wherein R<sup>1</sup> is phenyl, dichlorophenyl, bromophenyl, dichloromethylphenyl, 1-naphthyl, phenyl, methylphenyl, fluorophenyl, thiophenyl, chlorothiophenyl; R<sup>2</sup> is H or methyl; and R<sup>3</sup> is piperidinyl or N-methylpiperidinyl.

TABLE I

Para-substituted naphthalene compounds of the formula II wherein P is

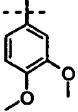

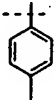

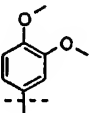

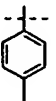

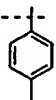





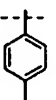

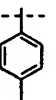

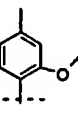

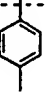



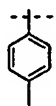

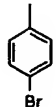
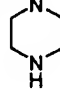
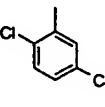
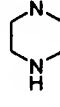
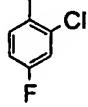
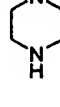
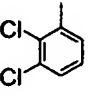
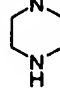
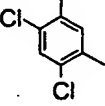
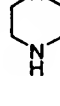
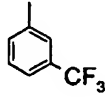
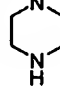
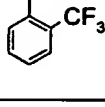
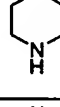
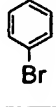
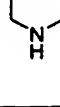


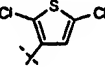

; and X, Y are H:



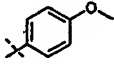

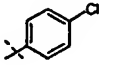

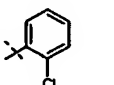

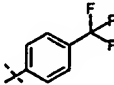

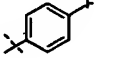

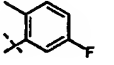

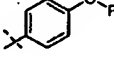

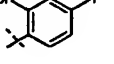



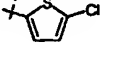

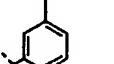

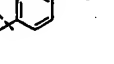

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























	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
1	N-(4-Methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			H
2	N-(2,4-Dimethoxyphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			H
3	N-(3,4-di-Fluorophenyl)-4-(4-methyl-1,4-diazepan-1-yl)-1-naphthalenesulfonamide, hydrochloride			H
4	N-(3-Fluorophenyl)-4-(4-methyl-1,4-diazepan-1-yl)-1-naphthalenesulfonamide, hydrochloride			H
5	4-(4-Ethyl-1-piperazinyl)-N-phenyl-1-naphthalenesulfonamide, hydrochloride			H
6	4-Hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl-N-(4-methylphenyl)-1-naphthalenesulfonamide, hydrochloride			H

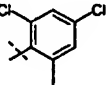

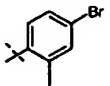

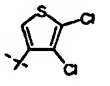

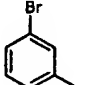

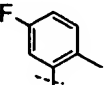

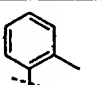

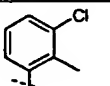

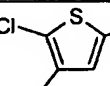

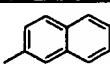

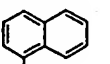

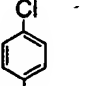

	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
7	N-(3,4-Dimethoxyphenyl)-4-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl-1-naphthalenesulfonamide, hydrochloride			H
8	4-(4-Ethyl-1-piperazinyl)-N-(4-methylphenyl)-1-naphthalenesulfonamide, hydrochloride			H
9	N-(3,4-Dimethoxyphenyl)-4-(3-methyl-1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			H
10	N-(4-Methylphenyl)-4-(4-methyl-1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			H
11	N-[4-(2,5-Diazabicyclo[2.2.1]hept-2-yl)-1-naphthyl]-4-methylbenzenesulfonamide, hydrochloride			H
12	N-(4-Methylphenyl)-4-(3-methyl-1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			H
13	N-(2-Naphthyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			H
14	N-Methyl-N-(4-methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			-CH <sub>3</sub>
15	4-(1,4-Diazepan-1-yl)-N-(4-methylphenyl)-1-naphthalenesulfonamide, hydrochloride			H
16	4-(1,4-Diazepan-1-yl)-N-(2-methoxy-4-methylphenyl)-1-naphthalenesulfonamide, hydrochloride			H
17	N-(2-Methoxy-4-methylphenyl)-4-(3,5-trimethyl-1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			H

	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
18	4-(4-Isopropyl-1-piperazinyl)-N-(4-methylphenyl)-1-naphthalenesulfonamide, hydrochloride			H
19	4-Bromo-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
20	2,5-di-Chloro-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride			H
21	2-Chloro-4-fluoro-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride			H
22	2,3-di-Chloro-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride			H
23	2,4-di-Chloro-5-methyl-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride			H
24	3-tri-Fluoromethyl-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride			H
25	2-tri-Fluoromethyl-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride			H
26	4-Bromo-N-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride.			CH <sub>3</sub>
27	Naphthalene-1-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride			H
28	2,5-Dichloro-thiophene-3-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride			H



	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
29	4-Methoxy-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
30	4-Chloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
31	2-Chloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
32	N-(4-Piperazin-1-yl-naphthalen-1-yl)-4-trifluoromethyl-benzenesulfonamide, hydrochloride			H
33	4-Fluoro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
34	5-Fluoro-2-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
35	4-Phenoxy-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
36	2-Bromo-4-iodo-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
37	Thiophene-2-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride			H
38	5-Chloro-thiophene-2-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride			H
39	3-Methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
40	4-Butyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide hydrochloride			H

	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
41	2,4,6-Trimethyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide hydrochloride			H
42	2,4,5-Trichloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
43	4-Iodo-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
44	2-Methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
45	3,4-Dichloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
46	5-Bromo-2-methoxy-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
47	2-Bromo-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
48	3-Chloro-2-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
49	2,6-Dichloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
50	3-Methoxy-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
51	3-Chloro-4-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
52	4-Bromo-2-fluoro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H

	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
53	2,4-Dichloro-6-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
54	4-Bromo-2-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride			H
55	4,5-Dichloro-thiophene-2-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride			H
56	N-Methyl-N-(4-bromo-2-methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			CH <sub>3</sub>
57	N-Methyl-N-(5-fluoro-2-methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			CH <sub>3</sub>
58	N-Methyl-N-(2-methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			CH <sub>3</sub>
59	N-Methyl-N-(3-chloro-2-methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			CH <sub>3</sub>
60	2,5-di-Chlorothiophen-3-yl-N-Methyl-N-(2,5-dichlorothiophen-3-yl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			CH <sub>3</sub>
61	N-Methyl-N-(1-naphthyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			CH <sub>3</sub>
62	N-Methyl-N-(1-naphthyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			CH <sub>3</sub>
63	N-Methyl-N-(4-chlorophenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			CH <sub>3</sub>

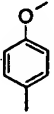




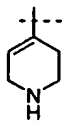
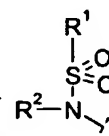
	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
64	N-Methyl-N-(4-methoxyphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride			CH <sub>3</sub>
65	5-Fluoro-2-methyl-N-{4-[(2R,5S)-2,5-dimethyl-1-piperazin-1-yl]-1-naphthyl}benzenesulfonamide, hydrochloride			H
66	5-Fluoro-2-methyl-N-[4-(1,2,3,6-tetrahydropyridin-4-yl)-1-naphthyl]benzenesulfonamide, hydrochloride			H

TABLE II

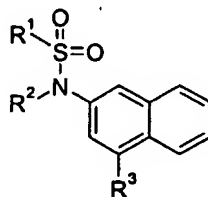
3-Substituted naphthalene compounds of the formula II wherein P is





; and X, Y are

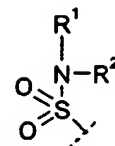
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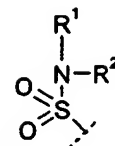
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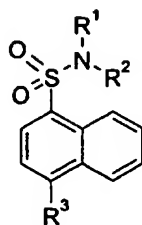







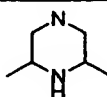

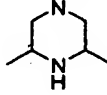






	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
67	N-[4-(4-Methyl-1-piperazinyl)-2-naphthyl]benzenesulfonamide, hydrochloride			H

10 TABLE III















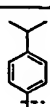











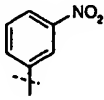
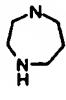
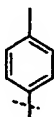
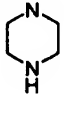
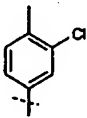
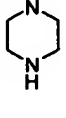
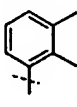
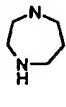
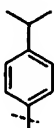
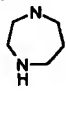
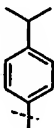
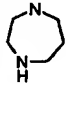
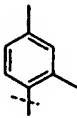
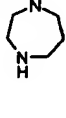
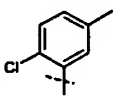

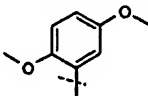

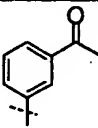
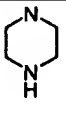
5-Substituted naphthalene compounds of the formula II wherein P is ; and X, Y and R<sup>4</sup> are H:



	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
68	4-Piperazin-1-yl-naphthalene-1-sulfonic acid phenylamide, hydrochloride			H
69	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-methoxy-phenyl)-amide, hydrochloride			H
70	4-( <i>cis</i> -3,5-Dimethyl-piperazin-1-yl)-naphthalene-1-sulfonic acid (2-methoxy-phenyl)-amide, hydrochloride			H
71	4-( <i>cis</i> -3,5-Dimethyl-piperazin-1-yl)-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide, hydrochloride			H
72	4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide, hydrochloride			H
73	4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid phenylamide, hydrochloride			H
74	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide, hydrochloride			H

	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
75	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-methylsulfanyl-phenyl)-amide, hydrochloride			H
76	4-Piperazin-1-yl-naphthalene-1-sulfonic acid methyl-naphthalen-1-yl-amide, hydrochloride			H
77	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2,3-dihydrobenzo[1,4]dioxin-6-yl)-methyl-amide, hydrochloride			CH <sub>3</sub>
78	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2,3-dihydrobenzo[1,4]dioxin-6-yl)-amide, hydrochloride			H
79	4-Piperazin-1-yl-naphthalene-1-sulfonic acid methyl-(2-methylsulfanyl-phenyl)-amide, hydrochloride			CH <sub>3</sub>
80	4-Piperazin-1-yl-naphthalene-1-sulfonic acid methyl-(3-trifluoromethyl-phenyl)-amide, hydrochloride			CH <sub>3</sub>
81	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-chloro-4-methyl-phenyl)-methyl-amide, hydrochloride			CH <sub>3</sub>
82	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-ethyl-phenyl)-methyl-amide, hydrochloride			CH <sub>3</sub>
83	4-(3,5-Dimethyl-piperazin-1-yl)-naphthalene-1-sulfonic acid (2-isopropyl-phenyl)-amide, hydrochloride			H
84	4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (2-isopropyl-phenyl)-amide, hydrochloride			H
85	4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-ethyl-phenyl)-amide, hydrochloride			H

	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
86	N-(2-Fluorophenyl)-4-piperazin-1-yl-naphthalene-1-sulfonamide, hydrochloride			H
87	4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-trifluoromethyl-phenyl)-amide, hydrochloride			H
88	N-(2,4-di-Fluorophenyl)-4-piperazin-1-yl-naphthalene-1-sulfonamide, hydrochloride			H
89	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-trifluoromethoxy-phenyl)-amide, hydrochloride			H
90	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-trifluoromethoxy-phenyl)-amide, hydrochloride			H
91	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-trifluoromethoxy-phenyl)-amide, hydrochloride			H
92	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-chloro-5-methyl-phenyl)-amide, hydrochloride			H
93	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (4-isopropyl-phenyl)-amide, hydrochloride			H
94	N-(3,5-di-Fluorophenyl)-4-piperazin-1-yl-naphthalene-1-sulfonamide, hydrochloride			H
95	1-[4-(3,4-Dihydroquinolin-1(2H)-ylsulfonyl)-1-naphthyl]piperazine, hydrochloride			H
96	4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-nitro-phenyl)-amide, hydrochloride			H
97	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-nitro-phenyl)-amide, hydrochloride			H

	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
98	4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-nitro-phenyl)-methyl-amide, hydrochloride			CH3
99	N-(4-methylphenyl)-4-piperazin-1-ynaphthalene-1-sulfonamide, hydrochloride			H
100	N-(3-chloro-4-methylphenyl)-4-piperazin-1-ynaphthalene-1-sulfonamide, hydrochloride			H
101	4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (2,3-dimethyl-phenyl)-methyl-amide, hydrochloride			CH3
102	4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (4-isopropyl-phenyl)-amide, hydrochloride			H
103	4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (4-isopropyl-phenyl)-methyl-amide, hydrochloride			CH3
104	4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (2,4-dimethyl-phenyl)-amide, hydrochloride			H
105	4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (2-chloro-5-methyl-phenyl)-amide, hydrochloride			H
106	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2,5-dimethoxy-phenyl)-amide, hydrochloride			H
107	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-acetyl-phenyl)-amide, hydrochloride			H



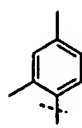
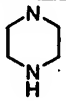
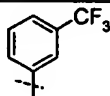

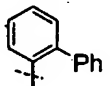

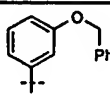

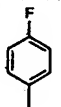



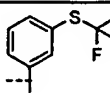

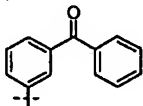

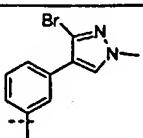

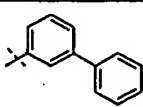

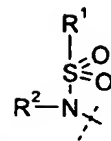
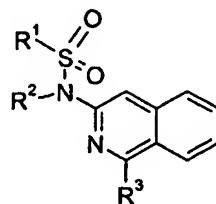
	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
108	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2,4-dimethyl-phenyl)-amide, hydrochloride			H
109	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-trifluoromethyl-phenyl)-amide, hydrochloride			H
110	4-Piperazin-1-yl-naphthalene-1-sulfonic acid biphenyl-2-ylamide, hydrochloride			H
111	4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-benzyloxy-phenyl)-amide, hydrochloride			H
112	N-(4-fluorophenyl)-4-piperazin-1-yl-naphthalene-1-sulfonamide, hydrochloride			H
113	N-(3-Ethylphenyl)-4-piperazin-1-yl-naphthalene-1-sulfonamide, hydrochloride			H
114	4-Piperazinyl-N-[3-(trifluoromethyl)phenyl]naphthalene-1-sulfonamide; hydrochloride			H
115	4-Piperazinyl-N-[3-benzoylphenyl]naphthalene-1-sulfonamide, hydrochloride			H
116	4-Piperazinyl-N-[3-(4-bromo-1-methyl-1H-pyrazol-3-yl)phenyl]naphthalene-1-sulfonamide, hydrochloride			H
117	4-Piperazinyl-N-[3-biphenylphenyl]naphthalene-1-sulfonamide, hydrochloride			H

TABLE IV

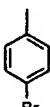
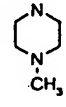
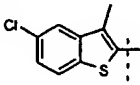



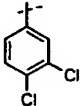
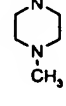






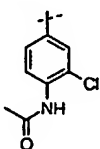

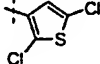





Meta-substituted isoquinoline compounds of the formula III wherein P is ; and X, Y are H:



5

	Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
118	N-[1-(4-methyl-1-piperazinyl)-3-isoquinoliny]benzenesulfonamide, hydrochloride			H
119	2,4-di-Fluoro-N-[1-(4-methyl-1-piperazinyl)-3-isoquinoliny]benzenesulfonamide, hydrochloride			H

120	4-Bromo-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride			H
121	5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-amide, hydrochloride			H
122	3-Chloro-2-methyl-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride			H
123	3,4-Dichloro-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride			H
124	4-Methyl-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride			H
125	3-Methoxy-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride			H
126	5-Chloro-thiophene-2-sulfonic acid [1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-amide, hydrochloride			H
127	N-{2-Chloro-4-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-ylsulfamoyl]-phenyl}-acetamide hydrochloride			H
128	2,5-Dichloro-thiophene-3-sulfonic acid [1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-amide, hydrochloride			H
129	N-[1-(4-Methyl-piperazin-1-yl)-isoquinolin-3-yl]-3-trifluoromethyl-benzenesulfonamide, hydrochloride			H

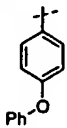
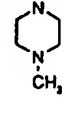
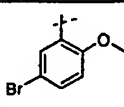
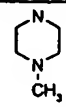
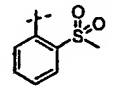
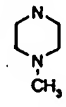
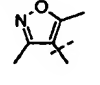

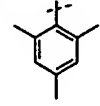
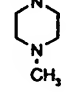
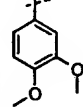
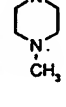
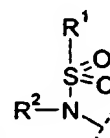
130	N-[1-(4-Methyl-piperazin-1-yl)-isoquinolin-3-yl]-4-phenoxy-benzenesulfonamide, hydrochloride			H
131	5-Bromo-2-methoxy-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride			H
132	2-Methanesulfonyl-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride			H
133	3,5-Dimethyl-isoxazole-4-sulfonic acid [1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-amide, hydrochloride			H
134	2,4,6-Trimethyl-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride			H
135	3,4-Dimethoxy-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride			H

TABLE V

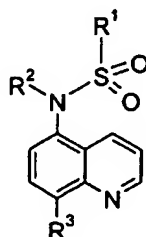
5-Substituted quinoline compounds of the formula IV wherein P is



; and X, Y are

H:

5



Compound name	R <sup>1</sup>	R <sup>3</sup>	R <sup>2</sup>
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

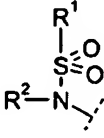
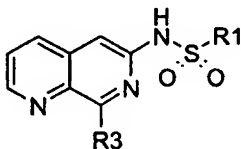






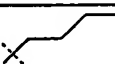



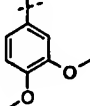

136	N-(8-{{2-(di-Methylamino)ethyl}amino}-5-quinoliny)benzenesulfonamide, hydrochloride			H
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TABLE VI

1,7-Naphthyridine compounds of the formula V wherein P is ; R<sup>2</sup> and X, Y are H:

5



	Compound name	R1	R3
137	4-Methyl-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic acid		
138	4-Bromo-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic acid		
139	N-(8-Piperazin-1-yl-1,7-naphthyridin-6-yl)naphthalene-1-sulfonamide, trifluoroacetic acid		
140	N-(8-Piperazin-1-yl-1,7-naphthyridin-6-yl)butane-1-sulfonamide, trifluoroacetic acid		
141	3-Trifluoromethyl-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic acid		
142	3,4-Dimethoxy-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic acid		

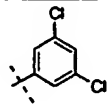
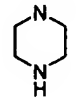




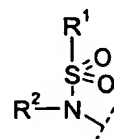
143	2,4-Dichloro-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic acid		
144	N-(8-Piperazin-1-yl-1,7-naphthyridin-6-yl)thiophene-2-sulfonamide, trifluoroacetic acid		
145	1-Phenyl-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)methanesulfonamide, trifluoroacetic acid		

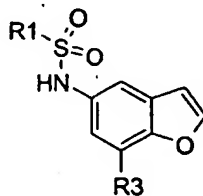
TABLE VII

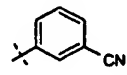

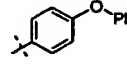



5-Substituted benzofuran compounds of the formula VI wherein P is


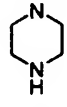
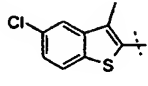
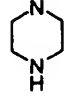

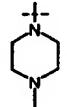

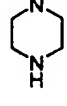
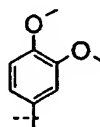
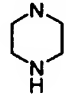
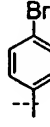
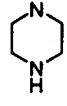
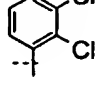
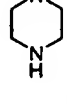
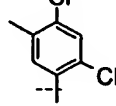
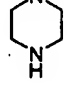
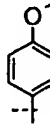
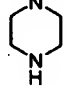
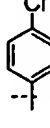
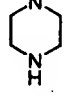


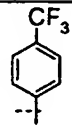
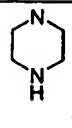
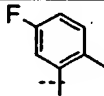



; R<sup>2</sup> and X,  
Y are H:

5



	Compound name	R1	R3
146	3-Cyanophenyl-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride		
147	4-Phenoxy-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride		
148	1-Naphthyl-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride		

149	N-(7-Piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride		
150	5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (7-piperazin-1-yl-benzofuran-5-yl)-amide, hydrochloride		
151	N-[7-(4-Methylpiperazin-1-yl)-1-benzofuran-5-yl]-benzenesulfonamide, hydrochloride		
152	4-Methyl-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride		
153	3,4-Dimethoxy-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride		
154	4-Bromo-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride		
155	2,3-Dichloro-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride		
156	2,4-Dichloro-5-methyl-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride		
157	4-Methoxy-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride		
158	4-Chloro-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride		

159	N-(7-Piperazin-1-yl-benzofuran-5-yl)-4-trifluoromethyl-benzenesulfonamide, hydrochloride		
160	5-Fluoro-2-methyl-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride		
161	5-Chloro-thiophene-2-sulfonic acid (7-piperazin-1-yl-benzofuran-5-yl)-amide, hydrochloride		

## METHODS FOR PREPARATION

- 5           The compounds according to the invention (Tables I, II, IV, V, VI) can be prepared starting from halo-nitro substituted bicyclic aromatic rings by base (potassium carbonate) catalyzed aromatic nucleophilic substitution of a halogen in the desired position of the central bicyclic ring with the diamine of choice ( $R^3$ ). Reduction of a nitro group properly positioned on the central bicyclic ring by Raney-Ni catalyzed reaction leads to the aniline that is
- 10   substituted further by sulfonylation with the alkyl- or aryl-sulfonylchloride of choice ( $R^1$ -SO<sub>2</sub>-Cl). Scheme 1 and Scheme 3

- The compounds according to the invention (Tables III) can be prepared starting from fluoro substituted bicyclic aromatic rings in which the sulfonylchloride functionality is
- 15   introduced by acid catalyzed sulfonylation. The sulfonyl group is reacted further with anilines of choice ( $R^1$ -NH<sub>2</sub>). The diamine group ( $R^3$ ) is introduced by base catalyzed aromatic nucleophilic substitution. Scheme 2

- The compounds according to the invention (Tables VII) can be prepared starting from
- 20   iodo substituted bicyclic aromatic rings. The diamine group ( $R^3$ ) is introduced by Palladium catalysed nucleophilic substitution. Reduction of a nitro group properly positioned on the central bicyclic ring by Raney-Ni catalyzed reaction leads to the aniline that is substituted



further by sulfonylation with the alkyl- or aryl-sulfonylchloride of choice ( $R^1-SO_2-Cl$ ).

#### Scheme 4

The chemicals used in the above-described synthetic routes may include, for example, solvents, reagents, catalysts, protecting group and deprotecting group reagents. The methods described above may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds of formula (I). In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing applicable compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2<sup>nd</sup> Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

Depending on the process conditions, the end products of the formula (I) are obtained either in neutral or salt form. Both the free base and the salts of these end products are within the scope of the invention.

Acid addition salts of the new compounds may in a manner known *per se* be transformed into the free base using basic agents such as alkali or by ion exchange. The free base obtained may also form salts with organic or inorganic acids.

In the preparation of acid addition salts, preferably such acids are used which form suitably therapeutically acceptable salts. Examples of such acids are hydrohalogen acids, sulfuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid,

hydroxymaleic acid, pyruvic acid, p-hydroxybenzoic acid, embonic acid, methanesulfonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, halogenbensenesulfonic acid, toluenesulfonic acid, mandelic acid or naphthalenesulfonic acid.

5        Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. All diastereomeric forms possible (pure enantiomers, tautomers, racemic mixtures and unequal mixtures of two enantiomers) are within the scope of the invention. Such compounds can also occur as cis- or trans-, *E*- or *Z*- double bond isomer forms. All  
10        isomeric forms are contemplated.

Pharmaceutical formulations are usually prepared by mixing the active substance, or a pharmaceutically acceptable salt thereof, with conventional pharmaceutical excipients. The formulations can be further prepared by known methods such as granulation, compression,  
15        microencapsulation, spray coating, etc.

This invention relates to a method of treatment or prophylaxis of obesity, type II diabetes, and/or disorders of the central nervous system. The method includes administering to a subject (e.g., a mammal, a human, a horse, a dog, or a cat) in need thereof an effective  
20        amount of one or more compounds of the formula (I) described above.

This invention also features a method for reducing body-weight (e.g., treating body-weight disorders). The method includes administering to a subject in need thereof an effective amount of a compound of the formula (I). As used herein, the term "body weight  
25        disorders" refers to the disorders caused by an imbalance between energy intake and energy expenditure, resulting in abnormal body (e.g., excessive) weights. Such body weight disorders include obesity.

Also within the scope of this invention is a method for modulating (e.g., inhibiting) 5-HT<sub>6</sub> receptor activity. The method includes administering to a subject in need thereof an effective amount of a compound of the formula (I).  
30

The methods delineated herein can also include the step of identifying that the subject is in need of treatment of obesity, type II diabetes, or disorders of the central nervous system, or in need of reducing body-weight.

5

"An effective amount" refers to an amount of a compound which confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. Usually the amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.2-20% by weight in preparations for parenteral use and preferably between 1 and 50% by weight in preparations for oral administration.

15 The typical daily dose of the active substance varies within a wide range and will depend on various factors such as, for example, the individual requirement of each patient and the route of administration. In general, oral and parenteral dosages will be in the range of 5 to 1000 mg per day of active substance, preferably 50 to 150 mg per day.

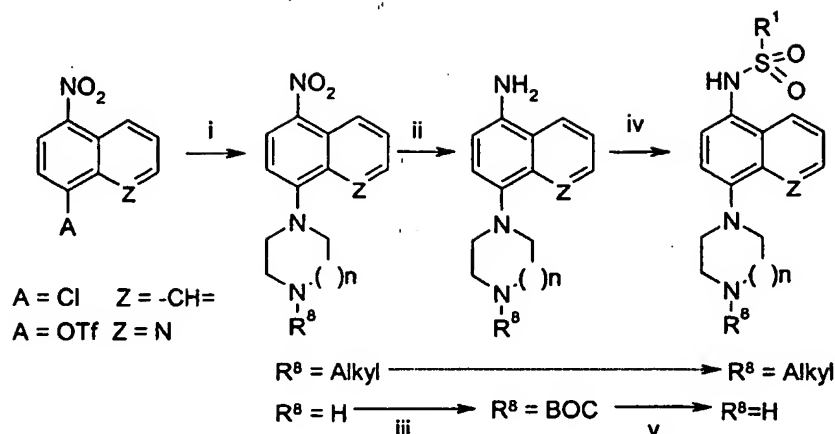
20 The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. All publications cited herein are hereby incorporated by reference in their entirety.

25

## EXAMPLES

### SYNTHESIS OF EXAMPLES AND INTERMEDIATES IN TABLE I

Scheme 1



In scheme 1, the following symbols are used: (i)  $\text{K}_2\text{CO}_3$ , DMF, diamine of choice; (ii)  $\text{H}_2$ ,  
 5 Raney-Ni or Pd/C, THF:Ethanol; (iii)  $(\text{BOC})_2\text{O}$ , NaOH; (iv)  $\text{R}^1\text{-SO}_2\text{-Cl}$ , Py,  $\text{CH}_2\text{Cl}_2$ ; (v) HCl  
 in diethyl ether; (vi) alkylhalides. TfO = trifluoromethanesulfonate.

#### General method A

##### *Reduction of nitronaphthalenes derivatives to naphthylamine derivatives*

10 To a solution of nitronaphthalenes derivatives (1 eq) in EtOH:THF (4:1) was added  
 Raney-Ni (~ 1.0 mL suspension in EtOH) followed by hydrazine monohydrate (6 eq). The  
 mixtures are stirred vigorously for 3 hours and then filtered through celite pretreated with  
 water. The filtrate was concentrated, followed by the addition of toluene. Purifications are  
 performed by flash column chromatography ( $\text{SiO}_2$ ,  $\text{CHCl}_3/\text{MeOH}/\text{NH}_3$  9:1:0.4% and 2 parts  
 15 of light petroleum) to obtain the free base of naphthylamine derivatives.

#### General method B

##### *Reaction of 4-nitro-chloronaphthalenes with diamines*

20 Diamines (1.2 eq) are added to a suspension of chloronaphthalenes derivatives (1 eq)  
 and  $\text{K}_2\text{CO}_3$  (3.5) in DMF. The suspensions are stirred at  $65^\circ\text{C}$  for 16 hours followed by  
 filtration. Elimination of volatiles to give a crude residue. The residues are purified by flash  
 chromatography ( $\text{SiO}_2$ ,  $\text{CHCl}_3 \rightarrow \text{CHCl}_3/10\% \text{ MeOH}/0.4\% \text{ aq. NH}_3$ ) to give the  
 corresponding products as free bases.

(a) *Intermediates for preparation of compounds in Tables I, II, IV and V according to Scheme 1*

5 **INTERMEDIATE 1**

*1-Methyl-4-(4-nitro-1-naphthyl)-1,4-diazepane* – To a suspension of 1-chloro-4-nitronaphthalene (1.0 g, 4.82 mmol) and K<sub>2</sub>CO<sub>3</sub> (2.0 g, 14.46 mmol) in DMF (10 mL) was added 1-methyl-1,4-diazepane (0.66 g, 5.78 mmol). The suspension was stirred at 65°C for 16 hours followed by filtration. Elimination of volatiles to give a crude residue. The residue  
10 was purified by flash chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>→CHCl<sub>3</sub>/10% MeOH/ 0.4% aq. NH<sub>3</sub>) to give 0.79 g (57 %) of the free base: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.85-8.75 (m, 1H), 8.35-8.25 (m, 1H), 8.20-8.12 (m, 1H), 7.70-7.60 (m, 1H), 7.55-7.45 (m, 1H), 6.97-6.90 (m, 1H), 3.70-3.55 (m, 4H), 2.83-2.71 (m, 4H), 2.44 (s, 3H), 2.09-1.97 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 157.47, 139.13, 129.26, 127.82, 127.66, 126.53, 125.69, 125.40, 123.94, 111.22, 58.37, 57.37, 55.44,  
15 54.71, 46.97, 27.88; MS (posES-FIA) m/z = found 285.1463, calc 285.1477.

**INTERMEDIATE 2**

*4-(4-Methyl-1,4-diazepan-1-yl)-1-naphthylamine* – To a solution of 1-methyl-4-(4-nitro-1-naphthyl)-1,4-diazepane (0.793 g, 2.78 mmol) in 40 mL of EtOH:THF (4:1) was  
20 added Raney-Ni (~ 1.0 mL suspension in EtOH) followed by hydrazine monohydrate (0.696 g, 13.9 mmol). The mixture was stirred vigorously for 3 hours and then filtered through celite pretreated with water. The filtrate was concentrated, followed by the addition of toluene. Purification by flash column chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 9:1:0.4% and 2 parts of light petroleum) gave 0.441 g (62%) of the free base: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.37-8.29 (m,  
25 1H), 7.85-7.76 (m, 1H), 7.55-7.40 (m, 2H), 7.07-7.01 (m, 1H), 6.75-6.68 (m, 1H), 3.96 (br s, 2H), 3.36-3.20 (m, 4H), 2.95-2.76 (m, 4H), 2.48 (s, 3H), 2.10-1.95 (m, 2H); MS (posESI) m/z = 256 (M+H).

**INTERMEDIATE 3**

30 *1-Ethyl-4-(4-nitro-1-naphthyl)piperazine* – To a mixture of 1-chloro-4-nitronaphthalene (0.794 g, 3.82 mmol), and K<sub>2</sub>CO<sub>3</sub> (0.791 g, 5.73 mmol) in DMF (3 mL) was

added N-ethyl piperazine (0.486 mL, 3.82 mmol). The mixture was heated in a microwave oven at 100W for 1 minute. The reaction mixture was allowed to cool down and the procedure was repeated 5 times. The mixture was filtered and concentrated. The crude product was purified by column chromatography ( $\text{SiO}_2$ ,  $\text{CHCl}_3 \rightarrow \text{CHCl}_3/\text{MeOH}/\text{NH}_3$  9:1:0.4 % to give 0.950 g (87%) of a reddish brown solid;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.75-8.70 (m, 1H), 8.30 (d,  $J=8.4$  Hz, 1H), 8.24-8.20 (m, 1H), 7.72-7.66 (m, 1H), 7.60-7.54 (m, 1H), 7.02 (d,  $J=8.4$  Hz, 1H), 3.32-3.24 (m, 4H), 2.85-2.70 (m, 4H), 2.54 (q,  $J=7.3$  Hz, 2H), 1.17 (tr,  $J=7.3$  Hz, 3); MS (posEI)  $m/z$  385 ( $\text{M}^+$ ).

#### 10 **INTERMEDIATE 4**

(*cis*)-3,5-Dimethyl-1-(4-nitro-1-naphthyl)piperazine – This compound was prepared from 1-chloro-4-nitronaphthalene (0.481 g, 2.32 mmol) and *cis*-2,6-dimethylpiperazine (0.481 g, 2.32 mmol) by the method described above, yield 0.554 g (84%) of the pure product as a reddish brown solid;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.76-8.71 (m, 1H), 8.30 (d,  $J=8.4$  Hz, 1H), 8.23-8.14 (m, 1H), 7.72-7.66 (m, 1H), 7.61-7.55 (m, 1H), 7.0 (d,  $J=8.4$  Hz, 1H), 3.45-3.37 (m, 2H), 3.35-3.25 (m, 2H), 2.55-2.47 (m, 2H), 1.17-1.4 (m, 6H); MS (posEI)  $m/z$  385 ( $\text{M}^+$ ).

#### **INTERMEDIATE 5**

20 3-Methyl-1-(4-nitro-1-naphthyl)piperazine – This compound was prepared from 1-chloro-4-nitronaphthalene (0.395 g, 1.90 mmol) and 2-methylpiperazine (0.395 g, 1.90 mmol) by the method described above: yield 0.470 g (84%) of the pure product as a solid;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.75-8.70 (m, 1H), 8.29 (d,  $J=8.55$  Hz, 1H), 8.24-8.20 (m, 1H), 7.72-7.65 (m, 1H), 7.61-7.55 (m, 1H), 7.00 (d,  $J=8.55$  Hz, 1H), 3.46-3.37 (m, 2H), 3.31-3.15 (m, 3H), 25 2.95-2.89 (m, 1H), 2.61-2.53 (m, 1H), 1.15 (d,  $J=6.4$  Hz, 3H); MS (EI)  $m/z$  271 ( $\text{M}^+$ ).

#### **INTERMEDIATE 6**

2-(4-Nitro-1-naphthyl)octahydropyrrolo[1,2-*a*]pyrazine – This compound was prepared from 1-chloro-4-nitronaphthalene (0.306 g, 1.47 mmol) and octahydropyrrolo[1,2-*a*]pyrazine (0.185 g, 1.47 mmol) by the method described above, yield 0.332 g (76%) of the pure product as a yellow oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.75-8.71 (m, 1H), 8.29 (d,  $J=8.5$  Hz, 1H),

8.23-8.20 (m, 1H), 7.72-7.67 (m, 1H), 7.60-7.55 (m, 1H), 7.05 (d,  $J=8.5$  Hz, 1H), 3.64-3.59 (m, 1H), 3.54-3.48 (m, 1H), 3.27-3.10 (m, 3H), 2.90-2.80 (m, 1H), 2.70-2.65 (m, 1H), 2.60-2.30 (m, 2H), 2.00-1.80 (m, 3H), 1.65-1.50 (m, 1H); MS (posESI)  $m/z$  298 (M+H).

5 **INTERMEDIATE 7**

*1-(4-Nitro-1-naphthyl)-1,4-diazepane* – To a solution of 1-chloro-4-nitronaphthalene (0.971 g, 4.68 mmol) and  $K_2CO_3$  (0.973 g, 7.10 mmol) in  $CH_3CN$  (5.0 mL) was added homopiperazine (0.711 g, 7.10 mmol). The reaction mixture was heated in a closed sealed vessel at 120°C in a microwave oven for 10 min. The suspension was filtered and  
10 concentrated. Purification by column chromatography ( $SiO_2$ ,  $CHCl_3 \rightarrow CHCl_3/MeOH$  9:1) gave 0.952 g of the pure product;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.80-8.74 (m, 1H), 8.29 (d,  $J=8.5$  Hz, 1H), 8.25-8.19 (m, 1H), 7.71-7.63 (m, 1H), 7.57-7.49 (m, 1H), 7.03 (d,  $J=8.5$  Hz, 1H), 3.57-3.48 (m, 4H), 3.18-3.10 (m, 4H), 2.10-1.95 (m, 2H); MS (posEI)  $m/z$  272 ( $M^+$ ).

15 **INTERMEDIATE 8**

*tert-Butyl 4-(4-nitro-1-naphthyl)-1-piperazinecarboxylate* – 1-Chloro-4-nitronaphthalene (2.7 g, 13 mmol), *tert*-butyl-1-piperazinecarboxylate (2.4 g, 13 mmol) and potassium carbonate (2 g) were heated together in DMSO (100 mL) at 90°C overnight. The solution was allowed to cool to room temperature and poured into water (500 mL). The  
20 product was collected by filtration and recrystallised from methanol/water to yield 2.8 g (60%) of the title compound; mp 158.2 °C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.52 (s, 9 H), 3.2 (br, 4 H), 3.75 (br, 4 H), 7.04 (d,  $J=8.53$  Hz, 1 H), 7.62 (t,  $J=7.02$  Hz, 1 H), 7.73 (t,  $J=7.02$  Hz, 1 H), 8.25 (d,  $J=8.53$  Hz, 1 H), 8.3 (d,  $J=8.54$  Hz, 1 H), 8.73 (d,  $J=8.53$  Hz, 1 H).

25 **INTERMEDIATE 9**

*1-tert-Butyl 4-(4-{bis[(4-methylphenyl)sulfonyl]amino}-1-naphthyl)-1-piperazinecarboxylate* – *tert*-Butyl 4-(4-nitro-1-naphthyl)-1-piperazinecarboxylate (1g, 2.8 mmol) in ethanol (200mL) was hydrogenated at atmospheric pressure over Pd/C (10%, 0.2g) for 3 hours after which time the uptake of hydrogen ceased. The solution was filtered and  
30 evaporated. The residue was dissolved in toluene (100 mL) and evaporated to give an off white solid. The solid was dissolved in acetonitrile (50 mL) containing 4-

dimethylaminopyridine (0.73 g). Toluene sulfonyl chloride (1.14g, 6 mmol) was added and the mixture stirred at 35°C overnight. Brine was added and the product extracted into ethyl acetate (2 x 100 mL). The organic extracts were dried over MgSO<sub>4</sub> and evaporated to give a pale brown solid which was re-crystallized from ethanol. Yield 1.04g (58%) of a white solid. Mp 176-178; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.40 (s, 9 H), 2.36 (s, 6 H), 3.0 (br, 4 H), 3.6 (br, 4 H), 6.81 (AB, *J* = 8.03 Hz, 1 H), 6.89 (AB, *J* = 8.03 Hz, 1 H), 7.17 (m, 1 H), 7.19 (d, *J* = 7.53 Hz, 4 H), 7.32 (m, 1 H), 7.45 (d, *J* = 8.53 Hz, 1 H), 7.70 (d, *J* = 8.54 Hz, 4 H), 8.03 (d, *J* = 8.03 Hz, 1 H).

#### 10 INTERMEDIATE 10

*1-tert-Butyl 4-(4-([(4-methylphenyl)sulfonyl]amino)-1-naphthyl)-1-piperazinecarboxylate* – *1-tert-Butyl 4-(4-{bis[(4-methylphenyl)sulfonyl]amino}-1-naphthyl)-1-piperazinecarboxylate* (1 g, 1.6 mmol) was dissolved in ethanol (50 mL). Potassium hydroxide (85%, 0.54 g) was added and the solution refluxed for 12 hours. The solution was poured into water (100 mL) and acidified with acetic acid (0.6 mL). The product precipitated and was collected by filtration, washed with water and dried. Yield 0.81g; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.36 (s, 9 H), 2.22 (s, 3 H), 2.8 (br, 4 H), 3.5 (br, 4 H), 6.47 (s, 1 H), 6.79 (d, *J* = 8.03 Hz, 1 H), 7.03 (d, *J* = 8.03 Hz, 2 H), 7.07 (d, *J* = 8.03 Hz, 1 H), 7.3 (m, 2 H), 7.47 (d, *J* = 8.53 Hz, 2 H), 7.69 (1, *J* = 9.04 Hz, 1 H), 8.03 (d, *J* = 7.02 Hz, 1 H).

#### INTERMEDIATE 11

*1-tert-Butyl 4-(4-{methyl[(4-methylphenyl)sulfonyl]amino}-1-naphthyl)-1-piperazinecarboxylate* – *1-tert-Butyl 4-(4-([(4-methylphenyl)sulfonyl]amino)-1-naphthyl)-1-piperazinecarboxylate* (0.1 g, 0.2 mmol) was dissolved in DMSO (5 mL) and potassium carbonate (0.2 g) and methyl iodide (0.1 g) were added. The mixture was stirred and heated at 85°C for 15 hours. The solution was poured into water (50 mL) and the product collected by filtration, washed with water and dried. Yield 0.078 g (78 %) of a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.60 (s, 9 H), 2.56 (s, 3 H), 3.1 (br, 4 H), 3.36 (s, 3 H), 3.7 (br, 4 H), 6.90 (AB, *J* = 8.03 Hz, 1 H), 6.97 (AB, *J* = 8.03 Hz, 1 H), 7.41 (d, *J* = 8.03 Hz, 2 H), 7.6 (m, 2 H), 7.75 (d, *J* = 8.29 Hz, 2 H), 8.3 (m, 2 H).



**INTERMEDIATE 12**

*5-Nitro-8-quinolinyl trifluoromethanesulfonate* - To a solution of 5-nitro-8-quinolinol (1.89 g, 9.40 mmol) and Et<sub>3</sub>N (6.60 mL, 4.70 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (125 mL) was added N-phenyl-trifluoromethanesulfonimide (5.06 g, 14.1 mmol). The mixture was stirred at room temperature for 16 hours and then more of added N-phenyl-trifluoromethanesulfonimide (1.0 equiv.) was added and the mixture was stirred for another 16 hours. The reaction mixture was washed with 10% aqueous NaHCO<sub>3</sub>, dried with K<sub>2</sub>CO<sub>3</sub>, filtered and concentrated. The crude residue was triturated in MeOH to give 1.2 g (40%) of the pure product: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.20-9.18 (m, 1H), 9.11-9.07 (m, 1H), 8.48-8.45 (m, 1H), 7.83-7.79 (m, 1H), 7.76-7.72 (m, 1H); MS (posEI-DIP) *m/z* 321 (M+H).

**INTERMEDIATE 13**

*8-(4-Methyl-1-piperazinyl)-5-nitroquinoline* - To a suspension of 5-nitro-8-quinolinyl trifluoromethanesulfonate (0.50 g, 1.56 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.43 g, 3.12 mmol) in CH<sub>3</sub>CN (6.0 mL) was added 1-methylpiperazine (0.19 mL, 1.71 mmol). The suspension was stirred at room temperature for 16 hours. The mixture was filtered and concentrated. Purification via flash column chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 9:1:0.4%) gave 0.509 g of the pure product: reversed phase HPLC >95% purity; MS (posESI) *m/z* 273 (M+H).

**INTERMEDIATE 14**

*tert-Buyl (2R,6S)-2,6-dimethyl-4-(4-nitro-1-naphthyl)-1-piperazinecarboxylate* - To a solution of cis-3,5-dimethyl-1-(4-nitro-1-naphthyl)piperazine (0.565 g, 1.98 mmol) and NaOH (0.198 g, 4.95 mmol) in THF:water (20 mL, 1:1) was added di-tert-butyl dicarbonate (1.30 g, 5.94 mmol) in THF (4 mL). The reaction mixture was stirred at room temperature for 4 hours followed by the addition of 3.0 equiv. of di-tert-butyl dicarbonate and 2.5 equiv. of NaOH. The mixture was stirred at room temperature for another 3 days. The mixture was concentrated and extracted with CHCl<sub>3</sub> (3 x 20 mL). The combined organic phases were dried with K<sub>2</sub>CO<sub>3</sub>, filtered and concentrated. The crude residue was purified by column

chromatography on silica using  $\text{CHCl}_3$  as eluent gave 0.200 g (26%) of the pure product as a solid brown solid: MS (posESI)  $m/z$  386 (M+H).

### INTERMEDIATE 15

5        *tert*-Butyl-2-methyl-4-(4-nitro-1-naphthyl)-1-piperazinecarboxylate was prepared from 3-methyl-1-(4-nitro-1-naphthyl)piperazine (0.436 g, 1.61 mmol) by the method described above: yield 0.552 g (92%) of the pure product as a yellow oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.73-8.70 (m, 1H), 8.34-8.30 (m, 1H), 8.28 (d,  $J=8.5$  Hz, 1H), 7.74-7.69 (m, 1H), 7.63-7.58 (m, 1H), 7.02 (d,  $J=8.5$  Hz, 1H), 4.50-4.442 (m, 1H), 4.10-4.03 (m, 1H), 3.52-3.39 (m, 2H),  
10    3.32-3.27 (m, 1H), 3.08-3.03 (m, 1H), 2.89-2.82 (m, 1H), 1.53 (s, 3H), 1.51 (s, 9H); MS (posESI)  $m/z$  372 (M+H).

### EXAMPLES OF COMPOUNDS ACCORDING TO THE INVENTION

15

#### EXAMPLE 1

##### 4-Methyl-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride

1-*tert*-Butyl 4-[(4-[(4-methylphenyl)sulfonyl]amino)-1-naphthyl]-1-piperazinecarboxylate (intermediate 10) (0.4g, 0.8mmol) was dissolved in THF (20mL) and  
20    treated with a 1N solution of HCl in diethyl ether (30 mL) for twelve hours. The product was collected as a pale pink solid. Yield 0.2g (60%). mp 181°C (dec);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  2.80 (s, 3 H), 3.1 (br, 4 H), 3.3 (br, 4 H), 7.00 (q,  $J = 8.06$  Hz, 2 H), 7.27 (ab,  $J = 8.30$  Hz, 2 H), 7.4-7.5 (m, 2 H), 7.53 (ab,  $J = 8.30$  Hz, 2 H), 7.99 (d,  $J = 8.06$  Hz, 1 H), 8.07 (d,  $J = 7.57$  Hz, 1 H), 9.2 (br, 2 H); MS (ESI+) for  $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$  Found  $m/z$  381.1499  $\text{M}^+$  Calc.  
25    381.1611.

#### EXAMPLE 2

##### 3,4-Dimethoxy-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride

*tert*-Butyl 4-(4-nitro-1-naphthyl)-1-piperazinecarboxylate (1 g, 2.8 mmol) in ethanol  
30    (200 mL) was hydrogenated at atmospheric pressure over Pd/C (10%, 0.2 g) for 3 hours after which time the uptake of hydrogen ceased. The solution was filtered and evaporated. The

residue was dissolved in toluene (100 mL) and evaporated to give an off white solid. The solid was dissolved in acetonitrile (50 mL) containing 4-dimethylaminopyridine (0.73 g). This solution was divided into three portions. To one portion was added 3,4-dimethoxybenzene sulfonyl chloride (0.24 g). The mixture was stirred for 4 hours at 40°C under nitrogen. Ethyl acetate (50 mL) was added and the solution washed with brine (2 x 100 mL). The organic phase was separated, dried over MgSO<sub>4</sub> and evaporation. Purification by flash chromatography (SiO<sub>2</sub>, Petrol:Ethyl acetate 1:1) afforded the butoxycarbonyl protected product which was dissolved in methanol (2 mL) and treated with a 1N solution of HCl in ethyl acetate (25 mL) for three hours. The product was precipitated with ether (200 mL) and collected as a pale pink solid, 45 mg (12 %). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 3.17 (br, 4 H), 3.35 (br, 4 H), 3.63 (s, 3 H), 3.78 (s, 3 H), 7.03 (d, *J* = 8.55 Hz, 1 H), 7.07 (ab, *J* = 13.92, 8.06 Hz, 2 H), 7.24 (dd, *J* = 8.30, 2.19 Hz, 1 H), 7.46 (m, 1 H), 7.51 (m, 1 H), 8.05 (d, *J* = 7.57 Hz, 1 H), 8.12 (d, *J* = 7.56 Hz, 1 H), 9.2 (br, 2 H), 9.93 (s, 1 H); MS (ESI+) for C<sub>22</sub> H<sub>25</sub> N<sub>3</sub> O<sub>4</sub> S *m/z* 427 (M+H)<sup>+</sup>.

15

### EXAMPLE 3

#### 3,4-di-Fluoro-N-[4-(4-methyl-1,4-diazepan-1-yl)-1-naphthyl]benzenesulfonamide, hydrochloride

To a solution of (intermediate 2) 4-(4-methyl-1,4-diazepan-1-yl)-1-naphthylamine (0.173 g, 0.676 mmol) and pyridine (0.450 mL, 4.73 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added a solution of 2,4-Di-fluorobenzenesulfonyl chloride (0.158 g, 0.743 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). The mixture was stirred at room temperature for 16 hours and then concentrated. The crude mixture was purified by column chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 9:1:0.4%). The free base was converted to its HCl-salt and recrystallized from MeOH and ether to give 0.227 g (79%) of the salt: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.23 (br s, 1H), 10.49 (s, 1H), 8.21-8.17 (m, 1H), 7.72-7.65 (m, 1H), 7.55-7.46 (m, 3H), 7.19-7.10 (m, 3H), 3.65-3.35 (m, 6H), 3.30-3.15 (m, 2H), 2.85-2.82 (m, 3H), 2.33-2.10 (m, 2H); MS (posES-FIA) *m/z* 432 (M+H).

## EXAMPLE 4

**3-Fluoro-N-[4-(4-methyl-1,4-diazepan-1-yl)-1-naphthyl]benzenesulfonamide, hydrochloride**

To a solution of (intermediate 3 after reduction according to Method A) 4-(4-methyl-1,4-diazepan-1-yl)-1-naphthylamine (0.173 g, 0.676 mmol) and pyridine (450  $\mu$ L, 4.73 mmol) in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was added 3-fluorobenzenesulfonyl chloride (0.145 g, 0.743 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL). The solution was stirred at room temperature for 16 hours and the volatiles were evaporated. The crude product was purified by column chromatography ( $\text{SiO}_2$ ,  $\text{CHCl}_3/\text{MeOH}/\text{NH}_3$  9:1:0.4%) to give 240 mg of the product as solid that was triturated with MeOH/ether to give 0.180 g (64%) of the free base which was converted to its HCl-salt:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  11.07 (br s, 1H), 10.28 (br s, 1H), 8.20-8.16 (m, 1H), 7.98-7.94 (m, 1H), 7.60-7.40 (m, 6H), 7.16-7.12 (m, 1H), 7.06-7.02 (m, 1H), 3.65-3.30 (m, partly obscured by solvent signal, HDO, 6H), 3.26-3.18 (m, 2H), 2.84 (s, 3H), 2.30-2.05 (m, 2H); MS (posES-FIA)  $m/z$  = 414 (M+H).

## EXAMPLE 5

**N-[4-(4-Ethyl-1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride**

The title compound was prepared from (intermediate 3 after reduction according to Method A) 4-(4-ethyl-1-piperazinyl)-1-naphthylamine (0.241 g, 0.945 mmol) and benzenesulfonyl chloride (0.121 mL, 0.945 mmol) by the method described above to yield HCl-salt 0.210 g (51%);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.19-8.15 (m, 1H), 7.94-7.90 (m, 1H), 7.70-7.66 (m, 2H), 7.56-7.46 (m, 2H), 7.44-7.36 (m, 3H), 7.19 (d,  $J=8.0$  Hz, 1H), 7.11 (d,  $J=8.0$  Hz, 1H), 3.75-3.40 (m, 6H), 3.34 (q,  $J=7.6$  Hz, 2H), 3.25-3.10 (m, 2H), 1.43 (tr,  $J=7.6$  Hz, 3H); MS(posEI)  $m/z$  387 ( $\text{M}^+$ ).

## EXAMPLE 6

**N-(4-Hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl-1-naphthyl)-4-methylbenzenesulfonamide, hydrochloride**

To a solution of (intermediate 6) 2-(4-nitro-1-naphthyl)octahydropyrrolo[1,2-a]pyrazine (0.160 g, 0.54 mmol) in 10 mL THF:EtOH (20 mL, 1:4) was added Raney-Ni (1.0 mL suspension in EtOH) followed by hydrazine hydrate (0.135 g, 2.70 mmol). The mixture

was stirred vigorously at room temperature for 16 hours and then filtered through celite pretreated with water. The filtrate was concentrated and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and pyridine (0.35 mL, 3.78 mmol) and *p*-toluenesulfonyl chloride (0.13 g, 0.54 mmol) were added to the solution. The reaction mixture was stirred at room temperature for 5 16 hours and then concentrated. The crude product was purified by column chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 9:1:0.4 %) to give 0.217 g (95%) of the free base which was converted to its HCl-salt: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.21-8.14 (m, 1H), 7.97-7.93 (m, 1H), 7.58-7.47 (m, 3H), 7.43-7.37 (m, 1H), 7.25-7.10 (m, 4H), 4.12-4.02 (m, 1H), 3.80-3.0 (m, partly obscured by solvent signal, 8H), 2.45-2.10 (m, 3H), 2.35 (s, 3H), 1.87-1.75 (m, 10 1H); MS (posEI) *m/z* 421 (M<sup>+</sup>).

#### EXAMPLE 7

##### N-(4-Hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl-1-naphthyl)-3,4-dimethoxybenzenesulfonamide, hydrochloride

15 The title compound was prepared from (intermediate 6) 2-(4-nitro-1-naphthyl)octahydropyrrolo[1,2-a]pyrazine (0.133 g, 0.447 mmol) by the method described above: yield 0.160 g (76%) of the pure product as the free base which was converted to its HCl-salt; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.20-8.16 (m, 1H), 7.96-7.92 (m, 1H), 7.54-7.48 (m, 1H), 7.43-7.38 (m, 1H), 7.30-7.26 (m, 1H), 7.23 (d, J=8.0 Hz, 1H), 7.16 (d, J=8.0 Hz, 1H), 7.09-20 7.07 (m, 1H), 6.95-6.92 (m, 1H), 3.83 (s, 3H), 3.82-3.0 (m, partly obscured by solvent signal, 10H), 3.62 (s, 3H), 2.50-2.10 (m, 2H); MS (posEI) *m/z* 467 (M<sup>+</sup>).

#### EXAMPLE 8

##### N-[4-(4-Ethyl-1-piperazinyl)-1-naphthyl]-4-methylbenzenesulfonamide, hydrochloride

25 To a solution of (intermediate 3 after reduction according to Method A) 4-(4-ethyl-1-piperazinyl)-1-naphthylamine 0.241 g, 0.945 mmol) and pyridine (0.534 mL, 0.945 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added *p*-toluenesulfonyl chloride (0.180 g, 0.945 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL). The mixture was stirred at room temperature for 16 hours followed by the addition of CH<sub>2</sub>Cl<sub>2</sub> (15 mL). The reaction mixture was washed with saturated aqueous NaHCO<sub>3</sub>, dried 30 with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude residue was purified by column chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>→CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 9:1:0.4%) to give a solid which was

converted to its HCl-salt: yield HCl-salt 0.372 g (88%); <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.20-8.15 (m, 1H), 7.97-7.93 (m, 1H), 7.58-7.54 (m, 2H), 7.53-7.47 (m, 1H), 7.43-7.37 (m, 1H), 7.25-7.20 (m, 2H), 7.18 (d, J=8.0 Hz, 1H), 7.10 (d, J=8.0 Hz, 1H), 3.80-3.10 (m, partly obscured by solvent signal, 10 H), 2.35 (s, 3H), 1.43 (tr, J=7.3 Hz, 3H); MS (posEI) *m/z* 409 (M<sup>+</sup>).

5

#### EXAMPLE 9

##### **3,4-Dimethoxy-N-[4-(3-methyl-1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride**

The title compound was prepared from (intermediate 8 after reduction according to Method A) tert-butyl 4-(4-amino-1-naphthyl)-2-methyl-1-piperazinecarboxylate (0.189 g, 0.55 mmol) and 3,4-dimethoxybenzenesulfonyl chloride (0.130 g, 0.55 mmol) by the method described above: yield HCl-salt 0.068 g (26%); <sup>1</sup>H NMR (CD<sub>3</sub>OD)

#### EXAMPLE 10

##### **4-Methyl-N-[4-(4-methyl-1-piperizinyl)-1-naphthyl]-1-benzenesulfonamide, hydrochloride**

To a solution of 4-(4-methyl-1-piperazinyl)-1-naphthylamine (prepared according to methods A and B) (0.099 g, 0.409 mmol) and pyridine (231 μL, 2.86 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added 4-methylbenzenesulfonyl chloride (0.078 g, 0.409 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL). The solution was stirred at room temperature for 16 hours and then washed with saturated aqueous NaHCO<sub>3</sub>, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude product was purified via column chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>→CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 9:1:0.4%) to give the pure base which was converted to its HCl-salt: yield 110 mg (62 %); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.86 (br s, 1H), 10.02 (s, 1H), 8.11-8.03 (m, 2H), 7.60-7.56 (m, 2H), 7.55-7.44 (m, 2H), 7.33-7.30 (m, 2H), 7.09-7.06 (m, 1H), 7.04-7.01 (m, 1H), 3.55-3.32 (m, 6H), 3.19-3.10 (m, 2H), 2.86 (s, 3H), 2.34 (s, 3H); MS (posES-FIA) *m/z* = 395.1665 (M+H)(calc 395.1667).

#### EXAMPLE 11

##### **4-Methyl-N-[4-(5-methyl-2,5-diazabicyclo[2,2,1]hept-2-yl]-naphthyl]benzenesulfonamide, hydrochloride**

To a solution of 4-(5-methyl-2,5-diazabicyclo[2,2,1]hept-2-yl)-1-naphtylamine (0.210 g, 0.829 mmol) (prepared according to methods A and B), pyridine (468  $\mu$ L, 5.80 mmol) in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was added 4-methylbenzenesulfonyl chloride (0.158 g, 0.829 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL). The solution was stirred at room temperature for 16 hours and then concentrated. The crude product was purified via column chromatography ( $\text{SiO}_2$ ,  $\text{CHCl}_3 \rightarrow \text{CHCl}_3/\text{MeOH}/\text{NH}_3$  9:1:0.4%) to give the pure base which was converted to its HCl-salt: yield 160 mg (43%);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  10.78 (br s, 1H), 9.90-9.88 (m, 1H), 8.02-7.98 (m, 2H), 7.58-7.55 (m, 2H), 7.49-7.41 (m, 2H), 7.33-7.30 (m, 2H), 7.06-7.03 (m, 1H), 6.93-6.90 (m, 1H), 4.38-4.30 (m, 3H), 3.65-3.60 (m, 3H), 2.90-2.87 (m, 1H), 2.86-2.83 (m, 3H), 2.36 (br s, 2H), 2.35 (s, 3H); MS (posES-FIA)  $m/z$  = 407.1655 ( $\text{M}+\text{H}$ ) (calc 407.1667).

#### EXAMPLE 12

##### 4-Methyl-N-[4-(3-methyl-1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride

To a solution of (intermediate 8 after resuction according to Method A) tert-butyl 4-(4-amino-1-naphthyl)-2-methyl-1-piperazinecarboxylate (0.189 g, 0.55 mmol) and pyridine (0.311 mL, 3.85 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was added toluenesulfonyl chloride (0.105 g, 0.55 mmol). The mixture was stirred at room temperature for 16 hours and then concentrated. The crude residue was purified by column chromatography ( $\text{SiO}_2$ , EtOAc:pentane 3:7). The pure intermediate was dissolved in small amount of MeOH and de-protected using ether saturated with HCl-gas. The precipitate was collected by filtration and triturated with MeOH and ether: yield HCl-salt 0.047 g (19%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.28-8.20 (m, 1H), 7.85-7.79 (m, 1H), 7.65-7.55 (m, 1H), 7.50-7.10 (m, partly obscured by solvent signal, 5H), 6.95-6.85 (m, 1H), 6.51 (br s, 1H), 4.50-4.25 (m, 1H), 4.05-3.85 (m, 1H), 3.52-3.33 (m, 1H), 3.28-3.05 (m, 2H), 2.97-2.85 (m, 1H), 2.82-2.67 (m, 1H), 2.85 (s, 3H), 1.52-1.47 (m, partly obscured by  $\text{H}_2\text{O}$  signal, 3H); MS (pos-ES)  $m/z$  = 395 ( $\text{M}+\text{H}$ ).

#### EXAMPLE 13

##### 2-N-[4-(1-Piperazinyl)-1-naphthyl]naphthalenesulfonamide, hydrochloride

To another portion of the solution of the reduced nitro compound was added 2-naphthalenesulfonyl chloride (0.23 g). The mixture was stirred for 4 hours at  $40^\circ\text{C}$  under nitrogen and worked up as above. The product obtained was identified as 1-tert-butyl 4-(4-

{bis[(2-naphthalene)sulfonyl]amino}-1-naphthyl)-1-piperazinecarboxylate. This bis sulfonamide was refluxed for 3 hours in ethanol (10 mL) containing NaOH (0.1 g). This solution was added to a solution of HCl in ethyl acetate (1N, 100 mL) and stirred overnight. The solution was evaporated to give the crude product which was purified by preparative  
5 hplc (CH<sub>3</sub>CN:H<sub>2</sub>O 10 % to 50 % gradient). Yield 47mg. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.05 (br, 4 H), 3.3 (br, 4 H), 7.0 (s, 2 H), 7.2-7.5 (m, 2 H), 7.55 (t, *J* = 7.9 Hz, 1 H), 7.62 (t, *J* = 6.9 Hz, 1 H), 7.76 (m, 1 H), 7.9-8.1 (m, 5 H), 8.21 (s, 1 H), 8.7 (br, 2 H)

#### EXAMPLE 14

10 **N,4-Dimethyl-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride**  
1-*tert*-Butyl 4-(4-{methyl[(4-methylphenyl)sulfonyl]amino}-1-naphthyl)-1-piperazinecarboxylate (intermediate 14 after reduction according to Method A) (75 mg, 0.15 mmol) was dissolved in methanol (5 mL) and treated with 1N HCl in ether (20 mL). After stirring overnight, the product precipitated and was collected by filtration, washed with ether  
15 and dried. Yield 60 mg (92%) of an off white solid.

#### EXAMPLE 15

##### **N-[4-(1,4-Diazepan-1-yl)-1-naphthyl]-4-methylbenzenesulfonamide, hydrochloride**

To a solution of (intermediate 7 after reduction according to Method A) 4-(1,4-  
20 diazepan-1-yl)-1-naphthylamine (0.399 g, 1.17 mmol), pyridine (661 μL, 8.19 mmol) and Et<sub>3</sub>N (329 μL, 2.34 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added 4-methylbenzenesulfonyl chloride (0.223 g, 1.17 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL). The solution was stirred at room temperature for 16 hours and then concentrated. The crude product was purified via column chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>→CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 9:1:0.4%) to give 0.360 g of the boc-protected  
25 compound. De-protection was accomplished by dissolving the intermediate in MeOH and then adding HCl-gas dissolved in ether. The precipitate was collected by filtration to give 0.143 g (28%) of the pure compound as the HCl-salt: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.00 (s, 1H), 9.28 (br s, 1H), 8.20-8.16 (m, 1H), 8.04-7.99 (m, 1H), 7.60-7.55 (m, 2H), 7.54-7.49 (m, 1H), 7.47-7.42 (m, 1H), 7.33-7.29 (m, 2H), 7.12 (d, *J* = 8.16 Hz, 1H), 7.01 (d, *J* = 8.16 Hz, 1H),  
30 3.42-3.31 (m, 6H), 3.20-3.16 (m, 2H), 2.34 (s, 3H), 2.14-2.08 (m, 2); MS (posES-FIA) *m/z* = 395.1667 (M+H) (calc 395.1667)



## EXAMPLE 16

***N*-[4-(1,4-Diazepan-1-yl)-1-naphthyl]-2-methoxy-4-methylbenzenesulfonamide, hydrochloride**

5 To a solution of (intermediate 7 after reduction according to Method A) 4-(1,4-diazepan-1-yl)-1-naphthylamine (0.399 g, 1.17 mmol), pyridine (661  $\mu$ L, 8.19 mmol) and Et<sub>3</sub>N (329  $\mu$ L, 2.34 mmol in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added 2-methoxy-4-methylbenzenesulfonyl chloride (0.258 g, 1.17 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL). The solution was stirred at room temperature for 16 hours and then concentrated. The crude product was dissolved in EtOH and powdered KOH was added to the solution. The mixture was stirred at 10 70°C for 16 hours. The suspension was concentrated and water was added. The solution was neutralized with 1N HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x20 mL). The combined organic phases were washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>→ CH<sub>2</sub>Cl<sub>2</sub>/MeOH (95:5) gave 0.432 g of a reddish brown solid. De-protection of the intermediate using MeOH ether saturated with HCl-gas gave 15 brown solid which was collected by filtration. The product was re-crystallized from MeOH/ether to give 109 mg (20%) of product as its HCl-salt: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  9.74 (s, 1H), 9.36 (br s, 2H), 8.20-8.14 (m, 2H), 7.55-7.45 (m, 3H), 7.44-7.42 (m, 1H), 7.16-7.09 (m, 2H), 7.02-7.00 (m, 1H), 6.75-6.74 (m, 1H), 3.85 (s, 3H), 3.42-3.27 (m, 6H), 3.18-3.14 (m, 2H), 2.31 (s, 3H), 2.14-2.07 (m, 2H); MS (posES-FIA) *m/z* = 425.1768 (M+H)(calc 425.1774)

## EXAMPLE 17

***N*-(2-Methoxy-4-methylphenyl)-4-(3, 5-trimethyl-1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride**

25 To a solution of (intermediate 4 after reduction according to Method A) 4-(2,6-dimethyl-1-piperazinyl)-1-naphthylamine (0.203 g, 0.563 mmol) and pyridine (322  $\mu$ L, 3.99 mmol) in DCM (3.0 mL) was added 4-methylbenzenesulfonyl chloride (0.107 g, 0.563 mmol) in DCM (1.0 mL). The solution was stirred at room temperature for 16 hours and then washed with saturated aqueous NaHCO<sub>3</sub>, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude intermediate was purified via column chromatography on silica using 30

CHCl<sub>3</sub>/CHCl<sub>3</sub>+10%MeOH + 0.4%NH<sub>3</sub> to give 0.230 g of the boc-protected intermediate.

Removal of the boc-group was accomplished by dissolving the intermediate in MeOH and then adding ether saturated with HCl-gas. The crude product was dissolved in DCM and then purified via column chromatography on silica using CHCl<sub>3</sub>/CHCl<sub>3</sub>+10%MeOH + 0.4% NH<sub>3</sub>

5 to give 156-mg (67%) of the pure base which was converted to its HCl- salt: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.01 (s, 1H), 9.86-9.78 (m, 1H), 9.14-9.00 (m, 1H), 8.13-8.10 (m, 1H), 8.05-8.02 (m, 1H), 7.58-7.55 (m, 2), 7.53-7.49 (m, 1H), 7.48-7.43 (m, 1H), 7.33-7.29 (m, 2H), 7.06 (d, J = 7.85 Hz, 1H), 7.02 (d, J = 8.17 Hz, 1H), 3.65-3.55 (m, 2H), 3.35-3.27 (m, 2H), 2.86-2.79 (m, 2H), 2.34 (s, 3H), 1.31 (d, J = 6.60 Hz, 6H); MS (posES-FIA) m/z = 409.1838  
10 (M+H)(calc 407.1824)

#### EXAMPLE 18

*N*-[4-(4-Isopropyl-1-piperiziny)-1-naphthyl]-4-methylbenzenesulfonamide, hydrochloride

15 To a solution of 4-(4-isopropyl-1-piperazinyl)-1-naphthylamine (0.209 g, 0.776 mmol) (prepared according to Methods A and B) and pyridine (438 μL, 5.43 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added 4-methylbenzenesulfonyl chloride (0.163 g, 0.850 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL). The solution was stirred at room temperature for 16 hours and the solid was collected by filtration as the HCl-salt to yield 0.236 g (66%); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ  
20 10.65 (br s, 1H), 9.95 (br s, 1H), 8.10-8.05 (m, 1H), 8.02-7.94 (m, 1H), 7.56-7.49 (m, 2H), 7.48-7.37 (m, 2H), 7.28-7.22 (m, 2H), 7.02-6.94 (m, 2H), 3.53-3.40 (m, 3H), 3.37-3.15 (m, 8H), 2.28 (s, 3H), 1.32-1.28 (m, 6H); MS (posES-FIA) m/z = 423.1972 (M+H)(calc 423.1980).

#### 25 EXAMPLE 19

**4-Bromo-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.21 (s, 1H), 9.12 (brs, 2H), 8.12 (d, J = 8.48 Hz, 1H), 7.97 (d, J = 8.16 Hz, 1H), 7.75-7.70 (m, 2H), 7.61-7.57 (m, 2H), 7.54-7.49 (m, 1H), 7.48-7.43 (m, 1H), 7.10-7.01 (M, 2h), 3.38-3.31 (M, 4H), 3.23-3.10 (M, 4H), MS (posESI) m/z = 446  
30 (M+H).

## EXAMPLE 20

**2,5-Dichloro-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.2 (br, 4 H), 3.4 (br, 4 H), 7.09 (s, 2 H), 7.54 (m, 2 H), 7.70 (m, 3 H), 8.10 (m, 2 H); MS (ESI+) for C<sub>20</sub> H<sub>19</sub> Cl<sub>2</sub> N<sub>3</sub> O<sub>2</sub> S *m/z* 436 (M+H)<sup>+</sup>.

5

## EXAMPLE 21

**2-Chloro-4-fluoro-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.1 (br, 4 H), 3.4 (br, 4 H), 7.01 (AB, *J* = 8.03 Hz, 1 H), 7.04 (AB, *J* = 8.03 Hz, 1 H), 7.27 (dt, *J* = 3.01, 8.53 Hz, 1 H), 7.5 (m, 2 H), 7.68 (dd, *J* = 2.51, 9.03 Hz, 1 H), 7.85 (dd, *J* = 6.52, 9.03 Hz, 1 H), 8.10 (d, *J* = 7.03 Hz, 1 H), 8.20 (d, *J* = 7.03 Hz, 1 H); MS (ESI+) for C<sub>20</sub> H<sub>19</sub> Cl F N<sub>3</sub> O<sub>2</sub> S *m/z* 420 (M+H)<sup>+</sup>.

10

## EXAMPLE 22

**2,3-Dichloro-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.1 (br, 4 H), 3.4 (br, 4 H), 7.01 (AB, *J* = 8.03 Hz, 1 H), 7.03 (AB, *J* = 8.03 Hz, 1 H), 7.42 (t, *J* = 7.78 Hz, 1 H), 7.50 (m, 2 H), 7.81 (dd, *J* = 1.51, 8.03 Hz, 1 H), 7.85 (dd, *J* = 1.51, 8.03 Hz, 1 H), 8.10 (dd, *J* = 6.52, 2.0 Hz, 1 H), 8.20 (dd, *J* = 7.53, 2.01 Hz, 1 H); MS (ESI+) for C<sub>20</sub> H<sub>19</sub> Cl<sub>2</sub> N<sub>3</sub> O<sub>2</sub> S *m/z* 436 (M+H)<sup>+</sup>.

15

## 20 EXAMPLE 23

**2,4-Dichloro,5-methyl-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 2.27 (s, 3 H), 3.15 (br, 4 H), 3.4 (br, 4 H), 7.07 (s, 2 H), 7.54 (m, 2 H), 7.79 (s, 1 H), 7.85 (s, 1 H), 8.13 (m, 1 H), 8.19 (m, 1 H); MS (ESI+) for C<sub>21</sub> H<sub>21</sub> Cl<sub>2</sub> N<sub>3</sub> O<sub>2</sub> S *m/z* 450 (M+H)<sup>+</sup>.

25

## EXAMPLE 24

**3-Trifluoromethyl-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.2 (br, 4 H), 3.4 (br, 4 H), 7.05 (AB, *J* = 8.03 Hz, 1 H), 7.10 (AB, *J* = 8.03 Hz, 1 H), 7.40 (t, *J* = 7.53 Hz, 1 H), 7.50 (t, *J* = 7.53 Hz, 1 H), 7.76 (t, *J* = 8.03 Hz, 1 H), 7.81 (s, 1 H), 7.88 (d, *J* = 8.53 Hz, 1 H), 7.95 (d, *J* = 8.03 Hz, 1 H), 7.99

30

(d,  $J = 8.03$  Hz, 1 H), 8.12 (d,  $J = 8.54$  Hz, 1 H); MS (ESI+) for C<sub>21</sub> H<sub>20</sub> F<sub>3</sub> N<sub>3</sub> O<sub>2</sub> S  $m/z$  436 (M+H)<sup>+</sup>.

#### EXAMPLE 25

5 **2-Trifluoromethyl-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  3.0 (br, 4 H), 3.4 (br, 4 H), 6.93 (s, 2 H), 7.36 (m, 1 H), 7.41 (m, 1 H), 7.64 (m, 2 H), 7.85 (dd,  $J = 2.01, 7.53$  Hz, 1 H), 7.90 (dd,  $J = 2.01, 7.03$  Hz, 1 H), 8.02 (d,  $J = 8.54$  Hz, 2 H).

10 **EXAMPLE 26**

**4-Bromo-N-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ ; 9.12 (brs, 2H), 8.22-8.07 (m, 2H), 7.89 (d,  $J = 8.44$  Hz, 2H), 7.74-7.58 (m, 4H), 7.10 (d,  $J = 7.91$  Hz, 1H), 6.89 (d, 8.18 Hz, 1H), 3.50 (s, 3H), 3.43-3.27 (m; obscured in part by solvent signal), MS (posESI)  $m/z = 460$  (M+H).

#### EXAMPLE 27

**Naphthalene-1-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ ; 9.00 (brs, 1H), 8.77-8.71 (m, 1H), 8.18 (d,  $J = 8.44$  Hz, 1H), 8.10-8.02 (m, 2H), 8.01-7.96 (m, 1H), 7.90 (d,  $J = 8.18$  Hz, 1H), 7.73-7.62 (m, 2H), 7.56-7.49 (m, 1H), 7.47-7.39 (m, 1H), 7.31-7.23 (m, 1H), 7.02-6.94 (m, 2H), 3.40-3.25 (m, obscured by solvent signal), 3.19-3.05 (m, 4H), MS (posESI)  $m/z = 418$  (M+H).

#### EXAMPLE 28

25 **2,5-Dichloro-thiophene-3-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ ; 10.52 (brs, 1H), 9.02 (brs, 2H), 8.19-8.12 (m, 1H), 8.01-7.94 (m, 1H), 7.60-7.47 (m, 2H), 7.23-7.12 (m, 3H), 3.43-3.28 (m, obscured in part by solvent signal), 3.25-3.10 (m, m, 4H), MS (posESI)  $m/z = 442$  (M+H).

30

#### EXAMPLE 29

**4-Methoxy-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 9.96 (s, 1H), 9.13 (brs, 1H), 8.15-8.08 (m, 1H), 8.06-7.99 (m, 1H), 7.65-7.57 (m, 2H), 7.55-7.42 (m, 2H), 7.12-6.97 (m, 4H), 3.43-3.29 (m, 4H), 3.24-3.10 (m, 4H), MS (posESI) m/z = 398 (M+H).

5

**EXAMPLE 30****4-Chloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.25 (brs, 1H), 9.03 (brs, 1H), 8.16-8.09 (m, 1H), 8.00-7.94 (m, 1H), 7.71-7.41 (m, 6H), 7.13-7.01 (m, 2H), 3.40-3.26 (m, obscured in part by solvent signal), 3.24-3.08 (m, 4H), MS (posESI) m/z = 402 (M+H).

10

**EXAMPLE 31****2-Chloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ; 8.24-8.12 (m, 2H), 7.90-7.83 (m, 1H), 7.60-7.43 (m, 3H), 7.32-7.27 (m, obscured in part by solvent signal, 1H), 7.09 (s, 1H), 7.04 (d, J = 8.44 Hz, 1H), 6.87-6.79 (m, 1H), 3.90-3.40 (m, 4H), 3.12-2.80 (m, 4H), MS (posESI) m/z = 402 (M+H).

15

**EXAMPLE 32****N-(4-Piperazin-1-yl-naphthalen-1-yl)-4-trifluoromethyl-benzenesulfonamide, hydrochloride**

20

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.40 (brs, 1H), 9.03 (brs, 1H), 8.12 (d, J = 7.65 Hz, 1H), 7.95-7.83 (m, 5 H), 7.55-7.39 (m, 2H), 7.13-7.02 (m, 2H), 3.40-3.30 (m, obscured in part by solvent signal), 3.23-3.09 (m, 4H), MS (posESI) m/z = 436 (M+H).

25 **EXAMPLE 33****4-Fluoro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.17 (brs, 1H), 9.18 (brs, 2H), 8.15-8.08 (m, 1H), 7.99-7.92 (m, 1H), 7.77-7.66 (m, 2H), 7.55-7.30 (m, 4H), 7.11-7.01 (m, 2H), 3.40-3.30 (m, obscured by solvent signal), 3.25-3.10 (m, 4H), MS (posESI) m/z = 386 (M+H).

30

**EXAMPLE 34**

**5-Fluoro-2-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.27 (brs, 1H), 9.19 (brs, 2H), 8.16-8.10 (m, 1H), 8.03-7.96 (m, 1H), 7.58-7.33 (m, 5H), 7.12-6.98 (m, 2H), 3.40-3.30 (m, obscured by solvent signal)  
5 3.24-3.10 (m, 4H), MS (posESI) m/z = 400 (M+H).

**EXAMPLE 35**

**4-Phenoxy-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.08 (s, 1H), 9.11 (brs, 2H), 8.18-8.07 (m, 1H), 7.98-7.89  
10 (m, 1H), 7.67-7.60 (m, 2H), 7.57-7.40 (m, 4H), 7.28-7.20 (m, 1H), 7.11 (s, 2H), 7.07-6.98 (m, 1H), 7.11 (s, 2H), 7.07-6.98 (m, 4H), 3.40-3.30 (m, obscured by solvent signal), 3.24-3.10 (m, 4H), MS (posESI) m/z = 460 (M+H).

**EXAMPLE 36**

**15 2-Bromo-4-iodo-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.45 (brs, 1H), 9.01 (brs, 2H), 8.28 (d, J = 1.58 Hz, 1H), 8.18-8.09 (m, 2H), 7.88-7.83 (m, 1H), 7.59-7.50 (m, 3H), 7.07 (s, 2H), 3.40-3.30 (m, obscured by solvent signal), 3.23-3.10 (m, 4H), MS (posESI) m/z = 572 (M+H).

20

**EXAMPLE 37**

**Thiophene-2-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.30 (s, 1H), 9.12 (brs, 1H), 8.17-8.09 (m, 1H), 8.00-7.92 (m, 1H), 7.89-7.85 (m, 1H), 7.56-7.38 (m, 3H), 7.18-7.06 (m, 3H), 3.40-3.30 (m, obscured by  
25 solvent signal), 3.25-3.15 (m, 4H), MS (posESI) m/z = 374 (M+H).

**EXAMPLE 38**

**5-Chloro-thiophene-2-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.43 (brs, 1H), 9.11 (brs, 2H), 8.19-8.111 (m, 1H), 8.02-7.95 (m, 2H), 7.29 (d, J = 3.95 Hz, 1H), 7.21-7.12 (m, 3H), 3.40-3.30 (m, obscured by solvent signal), 3.25-3.15 (m, 4H), MS (posESI) m/z = 408 (M+H).

5    **EXAMPLE 39**

**3-Methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 8.14-8.07 (m, 1H), 8.04-7.97 (m, 1H), 7.55-7.35 (m, 6H), 7.07-6.97 (m, 2H), 3.30-2.98 (m, obscured in part by solvent signal, 8H), 2.29 (s, 3H), MS (posESI) m/z = 442 (M+H).

10

**EXAMPLE 40**

**4-Butyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide hydrochloride:**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.05 (s, 1H), 9.20 (brs, 2H), 8.11 (d, J = 7.91 Hz, 1H), 7.93 (d, J = 8.18 Hz, 1H), 7.62-7.26 (m, 5H), 7.07 (s, 2H), 3.40-3.30 (m, obscured by solvent signal), 3.25-3.15 (m, 4H), 2.66-2.55 (m, obscured in part by solvent signal, 2H), 1.58-1.15 (m, 2H), 1.32-1.15 (m, 2H), 0.92-0.83 (m, 3H), MS (posESI) m/z = 427 (M+H).

**EXAMPLE 41**

20    **2,4,6-Trimethyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 9.92 (brs, 1H), 9.01 (brs, 2H), 8.15-8.09 (m, 1H), 8.05-7.98 (m, 1H), 7.55-7.42 (m, 2H), 7.09-6.94 (m, 4H), 3.40-3.30 (m, obscured by solvent signal), 3.25-3.15 (m, 4H) 2.85 (s, 6H), 2.22 (s, 3H), MS (posESI) m/z = 410 (M+H).

25

**EXAMPLE 42**

**2,4,5-Trichloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.68 (brs, 1H), 9.06 (brs, 1H), 8.22-8.08 (m, 2H), 8.18 (s, 1H), 7.88 (s, 1H), 7.61-7.52 (m, 2H), 7.09 (s, 2H), 3.40-3.30 (m, obscured by solvent signal), 3.25-3.15 (m, 4H), MS (posESI) m/z = 470 (M+H).

30

## EXAMPLE 43

**4-Iodo-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.22 (s, 1H), 9.06 (brs, 2H), 8.16-8.09 (m, 1H), 8.02-7.87  
5 (m, 3H), 7.58-7.39 (m, 4H), 7.18-6.98 (m, 2H), 3.40-3.30 (m, 4H), 3.25-3.10 (m, 4H), MS  
(posESI) m/z = 494 (M+H).

## EXAMPLE 44

**2-Methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride:**

10 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.13 (s, 1H), 9.15 (brs, 2H), 8.15-8.08 (m, 1H), 8.07-7.63  
(m, 1H), 7.70-7.63 (m, 1H), 7.61-7.23 (m, 2H), 3.41-3.27 (m, 4H), 3.24-3.09 (m, 4H), 2.55  
(s, obscured in part by solvent signal, 3H), MS (posESI) m/z = 382 (M+H).

## EXAMPLE 45

**3,4-Dichloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

15 MS (posESI) m/z = 436 (M+H)

## EXAMPLE 46

**5-Bromo-2-methoxy-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide,****hydrochloride**

20 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.13 (s, 1H), 9.10 (brs, 2H), 8.16-8.07 (m, 2H), 7.78-7.71  
(m, 1H), 7.59 (d, J = 2.64 Hz, 1H), 7.57-7.46 (m, 2H), 7.22-7.06 (m, 3H), 3.19 (s, 3H), 3.40-  
3.30 (m, obscured by solvent signal), 3.24-3.09 (m, 4H), MS (posESI) m/z = 476 (M+H).

## 25 EXAMPLE 47

**2-Bromo-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 9.37 (brs, 1H), 8.22-8.07 (m, 2H), 7.89-7.79 (m, 2H), 7.57-  
7.40 (m, 4H), 7.05 (s, 2H), 3.40-3.30 (m, obscured by solvent signal), 3.24-3.09 (m, 4H), MS  
(posESI) m/z = 446 (M+H).

30

## EXAMPLE 48



**3-Chloro-2-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 9.11 (brs, 1H), 8.17-8.09 (m, 1H), , 8.04-7.96 (m, 1H), 7.73-7.67 (m, 2H), 7.58-7.46 (m, 2H), 7.36-7.27 (m, 1H), 7.11-6.99 (m, 2H), 3.40-3.30 (m, obscured by solvent signal), 3.24-3.09 (m, 4H), 2.57 (s, 3H), MS (posESI) m/z = 416 (M+H).

**EXAMPLE 49**

**2,6-Dichloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.60 (s, 1H), 9.08 (brs, 1H), 8.18-8.06 (m, 2H), 7.66-7.44 (m, 5 H), 7.09 (s, 2H), 3.40-3.30 (m, obscured by solvent signal), 3.24-3.09 (m, 4H), MS (posESI) m/z = 436 (M+H).

**EXAMPLE 50**

**3-Methoxy-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.13 (s, 1H), 9.07 (brs, 2H), 8.15-8.08 (m, 1H), 8.02-7.95 (m, 1H), 7.56-7.36 (m, 3H), 7.28-7.22 (m, 1H), 7.19-7.02 (m, 4H), 3.69 (s, 3H), 3.40-3.30 (m, 4H), 3.24-3.10 (m, 4H), MS (posESI) m/z = 398 (M+H).

**EXAMPLE 51**

**3-Chloro-4-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.20 (brs, 1H), 9.12 (brs, 2H), 8.16-8.10 (m, 1H), 8.04-7.97 (m, 1H), 7.65-7.61 (m, 1H), 7.58-7.43 (m, 4H), 7.12-6.99 (m, 2H), 3.40-3.30 (m, obscured by solvent signal), 3.24-3.09 (m, 4H), 2.36 (s, 3H), MS (posESI) m/z = 416 (M+H).

**EXAMPLE 52**

**4-Bromo-2-fluoro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 10.59 (s, 1H), 9.17 (brs, 2H), 8.17-8.09 (m, 1H), 8.08-7.99 (m, 1H), 7.87-7.80 (m, 1H), 7.59-7.46 (m, 4H), 7.16-7.07 (m, 2H), 3.42-3.28 (, 4H), 3.24-3.08 (m, 4H), MS (posESI) m/z = 464 (M+H).

## EXAMPLE 53

**2,4-Dichloro-6-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

5  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$ ; 9.08 (brs, 2H), 8.18-8.04 (m, 2H), 7.73-7.69 (m, 1H), 7.60-7.42 (m, 3H), 7.14-7.04 (m, 2H), 3.40-3.30 (m, obscured by solvent signal), 3.24-3.09 (m, 4H), 2.80 (s, 3H), MS (posESI)  $m/z$  = 450 (M+H).

## EXAMPLE 54

10 **4-Bromo-2-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride**

$^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$ ; 10.24 (brs, 1H), 9.12 (brs, 2H), 8.17-8.10 (m, 1H), 8.05-7.98 (m, 1H), 7.68-7.65 (m, 1H), 7.58-7.46 (m, 4H), 7.10-6.96 (m, 2H), 3.40-3.30 (m, obscured by solvent signal), 3.24-3.09 (m, 4H), 2.53 (s, obscured in part by solvent signal, 3H), MS  
15 (posESI)  $m/z$  = 450 (M+H).

## EXAMPLE 55

**4,5-Dichloro-thiophene-2-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride**

20  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$ ; 8.97 (brs, 2H), 8.19-8.12 (m, 1H), 8.01-7.94 (m, 1H), 7.60-7.47 (m, 2H), 7.50 (s, 1H), 7.25-7.14 (m, 2H), 3.40-3.30 (m, obscured by solvent signal), 3.24-3.09 (m, 4H), MS (posESI)  $m/z$  = 442 (M+H).

## EXAMPLE 56

25 **N-Methyl-N-(4-bromo-2-methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride**

$^1\text{H}$  NMR (DMSO)  $\delta$  9.39 (br s, 2H), 8.23-8.13 (m, 1H), 8.09-7.99 (m, 1H), 7.75-7.56 (m, 5H), 7.13-7.02 (m, 2H), 3.41-3.18 (m, 8H), 3.26 (s, 3H), 2.25 (s, 3H); MS  $m/z$  (M+1)  
30 475.

## EXAMPLE 57

**N-Methyl-N-(5-fluoro-2-methylphenyl)-4-(1-pyperaziny)-1-naphthalenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO)  $\delta$  9.21 (br s, 2H), 8.23-8.14 (m, 1H), 8.04-7.97 (m, 1H), 7.64-7.45 (m, 5H), 7.13-7.03 (m, 2H), 3.43-3.17 (m, 8H), 3.29 (s, 3H), 2.21 (s, 3H); MS  $m/z$  (M+1) 414.

**EXAMPLE 58**

**N-Methyl-N-(2-methylphenyl)-4-(1-pyperaziny)-1-naphthalenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  8.26-8.19 (m, 1H), 8.11-8.05 (m, 1H), 7.87-7.81 (m, 1H), 7.62-7.49 (m, 3H), 7.40-7.32 (m, 2H), 7.13-7.03 (m, 2H), 3.57-3.49 (m, 4H), 3.34-3.30 (m, 7H), 2.30 (s, 3H); MS  $m/z$  (M+1) 396.

**EXAMPLE 59**

**N-Methyl-N-(3-chloro-2-methylphenyl)-4-(1-pyperaziny)-1-naphthalenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO)  $\delta$  9.52 (br s, 2H), 8.23-8.14 (m, 1H), 8.04-7.96 (m, 1H), 7.88-7.76 (m, 2H), 7.64-7.54 (m, 2H), 7.49-7.39 (m, 1H), 7.17-7.05 (m, 2H), 3.42-3.16 (m, 8H), 3.27 (s, 3H), 2.34 (s, 3H); MS  $m/z$  (M+1) 430.

**EXAMPLE 60**

**2,5-Dichlorothiophen-3-yl-Methyl-N-(2,5-dichlorothiophen-3-yl)-4-(1-pyperaziny)-1-naphthalenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO)  $\delta$  9.49 (br s, 1H), 8.24-8.13 (m, 1H), 8.07-7.98 (m, 1H), 7.67-7.55 (m, 2H), 7.33 (s, 1H), 7.24-7.07 (m, 2H), 3.44-3.18 (m, 10H); MS  $m/z$  (M+1) 456.

**EXAMPLE 61**

**N-Methyl-N-(1-naphthyl)-4-(1-pyperaziny)-1-naphthalenesulfonamide, hydrochloride**

The compound was prepared 1-*tert*-butyl-4-(4-{bis[(2-naphthalene)sulfonyl]amino}-1-naphthyl)-1-piperazinecarboxylate and potassium carbonate (120 mg, 0.87 mmol) in acetone (2 ml) was added iodomethane (44  $\mu$ l, 0.7 mmol) and the mixture was stirred at room

temperature over night. The mixture was diluted with acetonitrile, filtered and concentrated in vacuo. The residue was redissolved in DCM (3 ml) and treated with concentrated TFA (1 ml) at 0°C for 30 min and then allowed to reach room temperature. Removal of the solvents in vacuo and purification by reversed phase HPLC followed by treatment of the residue with an excess of 1M HCl in diethyl ether, gave the title compound (70 mg, 58%) as a solid. <sup>1</sup>H NMR (DMSO)  $\delta$  9.28 (br s, 2H), 8.44 (s, 1H), 8.24-8.07 (m, 5H), 7.80-7.56 (m, 5H), 7.07-7.00 (m, 1H), 6.88-6.81 (m, 1H), 3.41-3.18 (m, 8H), 3.27 (s, 3H); MS *m/z* (M+1) 432.

#### EXAMPLE 62

10 **N-Methyl-N-(1-naphthyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO)  $\delta$  9.25 (br s, 2H), 8.37-8.28 (m, 2H), 8.22-8.08 (m, 3H), 8.02-7.95 (m, 1H), 7.72-7.46 (m, 5H), 6.97 (s, 2H), 3.42-3.33 (m, 4H), 3.25 (s, 3H), 3.24-3.16 (m, 3H); MS *m/z* (M+1) 432.

#### 15 EXAMPLE 63

**N-Methyl-N-(4-chlorophenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride**

<sup>1</sup>H NMR (DMSO)  $\delta$  9.41 (br s, 2H), 8.23-8.05 (m, 2H), 7.73 (s, 4H), 7.67-7.56 (m, 2H), 7.13-7.03 (m, 1H), 6.92-6.85 (m, 1H), 3.42-3.19 (m, 8H), 3.22 (s, 3H); MS *m/z* (M+1) 416.

#### EXAMPLE 64

**N-Methyl-N-(4-methoxyphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride**

25 <sup>1</sup>H NMR (DMSO)  $\delta$  9.45 (br s, 2H), 8.22-8.11 (m, 2H), 7.69-7.57 (m, 4H), 7.21-7.14 (m, 2H), 7.09-7.03 (m, 1H), 6.86-6.81 (m, 1H), 3.87 (s, 3H), 3.41-3.19 (m, 8H), 3.16 (s, 3H); MS *m/z* (M+1) 412.

#### EXAMPLE 65

30 **5-Fluoro-2-methyl-N-{4-[(2R,5S)-2,5-dimethyl-1-piperazin-1-yl]-1-naphthyl}benzenesulfonamide, hydrochloride**

*Synthesis of (2R,5S)-2,5-Dimethyl-1-(4-nitro-1-naphthyl)piperazine* - A mixture of 1-chloro-4-nitronaphtalene (400 mg, 1.9 mmol), (2R,5S)-2,5-dimethylpiperazine (800 mg, 7 mmol) and potassium carbonate (1g, 7 mmol) in DMSO (4 ml) was stirred at 100°C over night followed by an additional 48 hours at room temperature. The reaction mixture was diluted with ethyl acetate and filtered. The filtrate was washed with brine and 2M NaOH solution and then dried with potassium carbonate. The residue was purified on a silica column, using 10% methanol in chloroform as an eluent, to give the title compound (220 mg, 41%) as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.68-8.53 (m, 2H), 8.31-8.26 (m, 1H), 7.76-7.59 (m, 2H), 7.30-7.24 (m, 1H), 3.32-3.87 (m, 4H), 2.96-2.82 (m, 1H), 2.44-2.32 (m, 1H), 1.14-1.04 (m, 3H), 0.99-0.89 (m, 3H); MS m/z (M+1) 286.

*Synthesis of tert-Butyl (2R,5S)-2,5-dimethyl-1-(4-nitro-1-naphthyl)piperazine-1-carboxylate* - To a stirred solution of (2R,5S)-2,5-Dimethyl-1-(4-nitro-1-naphthyl)piperazine (220 mg, 0.77 mmol) in DCM (2 ml) was added, at 0°C, BOC-anhydride dissolved in DCM (2 ml). The solution was stirred for 15 min and was then allowed to reach room temperature. Water was added and the solution was extracted with DCM. The organic phase was separated and dried with potassium carbonate to give the title compound (300 mg, 100%) as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.75-8.67 (m, 1H), 8.30-8.17 (m, 2H), 7.70-7.55 (m, 2H), 6.93-6.86 (m, 1H), 4.60-4.50 (m, 1H), 3.97-3.65 (m, 4H), 2.90-2.73 (m, 1H), 1.49 (s, 9H), 1.41-1.36 (m, 3H), 0.99-0.87 (m, 3H); MS m/z (M+1) 386.

*Synthesis of 5-Fluoro-2-methyl-N-{4-[(2R,5S)-2,5-dimethyl-1-]piperazin-1-yl-1-naphthyl}benzenesulfonamide hydrochloride salt* - A mixture of tert-butyl (2R,5S)-2,5-dimethyl-1-(4-nitro-1-naphthyl)piperazine-1-carboxylate (300 mg, 0.78 mmol) and 10% Pd on carbon (approx. 0.1 mmol) in methanol (10 ml) was stirred in an hydrogen atmosphere over night. The mixture was filtered through a pad of Celite and the solvent evaporated. The crude aniline was dissolved in DCM (2 ml) and pyridine (0.5 ml) and 5-fluoro-2-methylbenzenesulfonyl chloride (97 µl, 0.67 mmol) was added slowly to the solution. After stirring for 2 hours water was added and the solution was extracted with DCM, the organic phase separated and dried using potassium carbonate. Removal of the solvents in vacuo gave a residue which was dissolved in DCM (3 ml) and treated with concentrated TFA (2 ml) at 0°C. The stirred solution was allowed to reach room temperature after which the solvents were removed in vacuo to give, after purification by reversed phase HPLC and treatment

with an excess of 1M HCl in diethyl ether, the title compound (30 mg, 9 %) as a solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 0.85 (d, J=6.07 Hz, 3 H) 1.31 (d, J=6.60 Hz, 3 H) 2.47 (s, 3 H) 2.83 (m, 1 H) 3.15 (m, 2 H) 3.49 (m, 2 H) 3.67 (m, 1 H) 7.21 (m, 4 H) 7.47 (m, 3 H) 7.97 (m, J=7.92 Hz, 1 H) 8.44 (d, J=8.44 Hz, 1 H) MS m/z 428 (M+1).

5

## EXAMPLE 66

**5-Fluoro-2-methyl-N-[4-(1,2,3,6-tetrahydropyridin-4-yl)-1-naphthyl]benzenesulfonamide, hydrochloride**

*5-Fluoro-2-methyl-N-[4-bromo-1-naphthyl]benzenesulfonamide* - 4-Bromo-1-naphthylamine (0.96 g, 4.33 mmol) was dissolved in DCM (10 mL) before pyridine (1 mL) was added. 5-Fluoro-2-methylbenzenesulfonyl chloride was added neat and the reaction mixture was stirred for 16 h. HCl (1 M, 1 mL) was added to the reaction mixture. The organic phase was filtered through a Silica plug using DCM as eluent. The solvent was evaporated. The obtained crude product was purified by flash-chromatography using MeOH (10%) in pentane, to give the desired product as a tar. To increase the purity, the product was purified by recrystallising (EtOAc/hexanes). This gave the product with a purity of 95%. <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 8.22 (d, J=8.98 Hz, 1H), 7.92 (d, J=7.92 Hz, 1H), 7.64-7.51 (m, 4H), 7.25-7.23 (m, 1H), 7.21-7.05 (m, 2H), 6.84 (br.s, 1H, N-H), 2.55 (s, 3H); MS (ESI+) for C<sub>17</sub>H<sub>13</sub>BrFN<sub>2</sub>O<sub>2</sub>S m/z 394.263 (M+H)<sup>+</sup>.  
MS (ESI-) for C<sub>17</sub>H<sub>13</sub>BrFN<sub>2</sub>O<sub>2</sub>S m/z 394.263 m/z (M-H)<sup>-</sup>.

20

*5-Fluoro-2-methyl-N-[4-(4-(tert-butoxycarbonyl)-1-hydroxypiperidin-1-yl)-1-naphthyl]benzenesulfonamide* - 5-Fluoro-2-methyl-N-[4-bromo-1-naphthyl]benzenesulfonamide (0.32 g, 0.812 mmol) was dissolved in dry THF (1m mL) under N<sub>2</sub>(g). The reaction flask was cooled to -78 °C before n-BuLi (1.5 mL, 2.4 mmol) was added. The reaction mixture turned green. The reaction mixture was stirred for 5 minutes before a solution of tert-butyl 4-oxopiperidine-1-carboxylate (0.34 g, 1.7 mmol) was added during 10 s. The resulting reaction mixture was stirred and slowly reaching -30 °C after 3h. Water dissolved in THF was added and the reaction flask was brought to RT. Brine and EtOAc was added. The phases were separated and the organic phase was dried (MgSO<sub>4</sub>).  
The obtained crude product was purified by reverse-phase (using the gradient 40→90). This gave 0.17 g of the desired product. Purity 95%. <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ 8.91-8.87 (m,

30

1H), 7.97-7.93 (m, 1H), 7.63-7.59 (m, 1H), 7.53-7.45 (m, 2H), 7.35 (d, J = 8.1 Hz, 1H), 7.28-7.21 (m, 1H), 7.16-7.09 (m, 2H), 7.14 (br.s, 1H, N-H), 6.85 (br.s, 1H, O-H), 4.07-3.98 (m, 2H), 3.41-3.31 (m, 2H), 2.59 (s, 3H), 2.17-2.08 (m, 4H), 1.46 (s, 9H); MS (ESI+) for C27 H31 F N2 O5 S m/z 514.615 (M+H)<sup>+</sup>. Nothing; MS (ESI-) for C27 H31 F N2 O5 S m/z  
 5 514.615 (M-H)<sup>-</sup> 513.1.

The final product was obtained as following: 5-Fluoro-2-methyl-N-[4-(4-(tert-butoxycarbonyl)-1-hydroxypiperidin-1-yl)-1-naphthyl]benzenesulfonamide (0.022 g, 0.043 mmol) was dissolved in formic acid (5 mL) and stirred at RT for 24 h. HPLC showed complex reaction mixture. The reaction mixture was stirred at 100 °C for 4 h. One compound  
 10 was seen on HPLC. The solvent was evaporated. The crude was transformed to the HCl salt (0.020 g) for the desired product, purity 98%. <sup>1</sup>H NMR (270 MHz, CD<sub>3</sub>OD) δ 8.05-7.97 (m, 2H), 7.55-7.43 (m, 3H), 7.33-7.30 (m, 1H), 7.24-7.17 (m, 3H), 5.97 (br.s, 1H), 3.90-3.88 (m, 2H), 3.56-3.52 (m, 2H), 2.73-2.70 (m, 2H), 2.53 (s, 3H); MS (ESI+) for C22 H21 F N2 O2 S HCl m/z 396.13 + 35.98 (M+H)<sup>+</sup> 397.2; MS (ESI-) C22 H21 F N2 O2 S HCl m/z 396.13 +  
 15 35.98 (M-H)<sup>-</sup> 395.3.

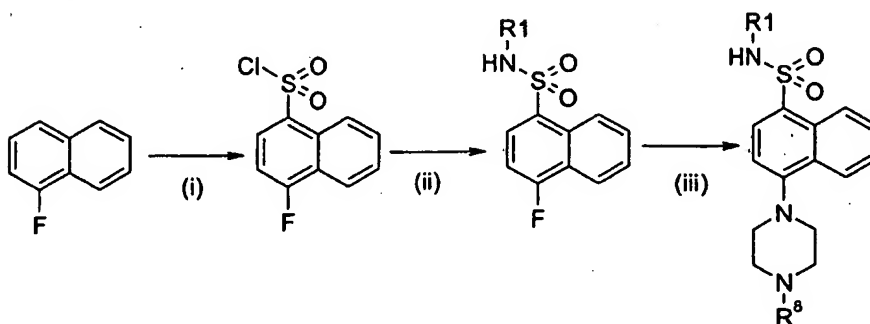
## SYNTHESIS OF EXAMPLE IN TABLE II

### EXAMPLE 67

20 **N-[4-(4-Methyl-1-piperazinyl)-2-naphthyl]benzenesulfonamide, hydrochloride**  
 To a solution of 1-(4-dimethyl-1-piperazinyl)-3-naphthylamine (0.230 g, 0.951 mmol) and pyridine (537 μL, 6.66 mmol) in DCM (3.0 mL) was added benzenesulfonyl chloride (0.168 g, 0.951 mmol) in DCM (1.0 mL). The reaction mixture was stirred at room temperature for 16 hours and then and then concentrated. The crude intermediate was first  
 25 purified via column chromatography on silica using CHCl<sub>3</sub>/CHCl<sub>3</sub>+10%MeOH + 0.4%NH<sub>3</sub> and then by preparative HPLC to give the pure base which was converted to its HCl-salt (yield 53% as HCl-salt): <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 10.76 (br s, 1H), 10.50 (s, 1H), 7.98-7.94 (m, 1H), 7.85-7.81 (m, 2H), 7.76-7.73 (m, 1H), 7.60-7.56 (m, 1H), 7.55-7.51 (m, 2H), 7.30 (d, J = 1.60 Hz, 1H), 6.99 (d, J = 1.88 Hz, 1H), 3.58-3.48 (m, 2H), 3.42-3.25 (m, m, partly  
 30 obscured by HDO signal, 4H), 3.12-3.00 (m, 2H), 2.86 (s, 3H); MS (posES-FIA) m/z = 381.15 24 (M+H)(calc 381.1511)

## SYNTHESIS OF INTERMEDIATES AND EXAMPLES IN TABLE III

Scheme 2



In scheme 2, the following reagents are used: (i) Chlorosulfonic acid, trifluoroacetic acid; (ii)  $R^1\text{-NH}_2$ , pyridine (1:4); (iii) diamines of choice and DMSO.

**INTERMEDIATE 16**

10 **4-Fluoro-naphthalene-1-sulfonyl chloride** – An emulsion of 1-fluoronaphthalene (4.00 g, 27 mmol) in TFA (19.5 mL) was stirred on an ice-bath. Chlorosulfonic acid (4.33 mL, 65 mmol) was added dropwise over 30 min. The ice-bath was removed and the reaction slurry stirred at rt for 2 h. Pouring the reaction mixture on 29 mL ice-cold water gave a white precipitate, which was filtered and washed with cold water. After drying, 4.50 g of white  
 15 solid (67%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.80 (d, 1H), 8.39 (dd, 1H), 8.28 (d, 1H), 7.88 (t, 1H), 7.76 (t, 1H), 7.26 (t, 1H); MS (EI) 244 (M). Purity (HPLC, Hichrom 200x4.6 mm I.D.) >98%.

**General method C**

20 **4-Fluoro-naphthalene-1-sulfonic acid phenylamide, 4-fluoro-naphthalene-1-sulfonic acid (2-methoxy-phenyl)-amide and 4-fluoro-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide** – Three reaction flasks with 4-fluoro-naphthalene-1-sulfonyl chloride (489 mg, 2.00 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) were treated with aniline (224 mg, 2.40 mmol), *o*-anisidine (296 mg, 2.40 mmol) and *m*-chloroaniline (306 mg, 2.40 mmol), respectively. Pyridine (0.5 mL)  
 25 was added and the reaction mixtures stirred for 3 h at rt. Dilution with ethyl acetate (50 mL)



followed by washing with 1 M HCl (3x50 mL), drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation gave 586 mg of 4-fluoro-naphthalene-1-sulfonic acid phenylamide (97%), 629 mg of 4-fluoro-naphthalene-1-sulfonic acid (2-methoxy-phenyl)-amide (95%) and 656 mg of 4-fluoro-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide (97%) as pink to red solids.

5

**INTERMEDIATE 17**

*4-Fluoro-naphthalene-1-sulfonic acid phenylamide*:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.66 (d, 1H), 8.20 (d, 1H), 8.15 (dd, 1H), 7.74 (t, 1H), 7.66 (t, 1H), 7.03-7.15 (m, 4H), 6.89 (d, 2H), 6.60 (bs, 1H); MS (CI) 299.8 ( $\text{M} - \text{H}$ ) $^+$ ; Purity (HPLC, Hichrom 200x4.6 mm I.D.) >98%.

10

**INTERMEDIATE 18**

*4-Fluoro-naphthalene-1-sulfonic acid (2-methoxy-phenyl)-amide*:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.70 (d, 1H), 8.16 (d, 1H), 8.12 (dd, 1H), 7.71 (t, 1H), 7.63 (t, 1H), 7.42 (d, 1H), 7.16 (bs, 1H), 7.06 (t, 1H), 6.95 (t, 1H), 6.83 (t, 1H), 6.56 (d, 1H), 3.30 (s, 3H); MS (CI) 330.2 ( $\text{M} - \text{H}$ ) $^+$ ; Purity (HPLC, Hichrom 200x4.6 mm I.D.) >98%.

15

**INTERMEDIATE 19**

*4-Fluoro-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide*:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.64 (d, 1H), 8.18-8.22 (m, 2H), 7.76 (t, 1H), 7.68 (t, 1H), 7.14 (dd, 1H), 7.06 (t, 1H), 7.02 (d, 1H), 6.97 (t, 1H), 6.78 (d, 1H), 6.67 (bs, 1H); MS (CI) 334.2 ( $\text{M} - \text{H}$ ) $^+$ ; Purity (HPLC, Hichrom 200x4.6 mm I.D.) >98%.

20

**25 General procedure D**

General procedure for preparation of compounds according to Examples 68-74:

Solutions of 4-fluoro-naphthalene-1-sulfonic acid (2-methoxy-phenyl)-amide (60 mg, 0.20 mmol), 4-fluoro-naphthalene-1-sulfonic acid (2-methoxy-phenyl)-amide (66 mg, 0.20 mmol) and 4-fluoro-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide (67 mg, 0.20 mmol) in DMSO (2 mL) were treated with piperazine (86 mg, 1.0 mmol), homopiperazine (100 mg, 1.0 mmol) and cis-2,6-dimethyl piperazine (114 mg, 1.0 mmol) in eight reaction

30

combinations. The reaction mixtures were stirred at 100°C for 3 h, diluted with ethyl acetate (50 mL), washed with sat. Na<sub>2</sub>CO<sub>3</sub> (3x50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated with an excess of HCl in ether, giving the hydrochlorides. No purification was necessary for compounds 20-23, while compounds 24-27 were purified with HPLC (YMC combiprep ODS-AQ, 50x20mm I.D.).

#### EXAMPLE 68

##### 4-Piperazin-1-yl-naphthalene-1-sulfonic acid phenylamide, hydrochloride

86 mg (95% yield) of a white solid. <sup>1</sup>H NMR (DMSO, 400 MHz) δ 9.52 (bs, 1H), 8.72 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 7.71 (t, 1H), 7.64 (t, 1H), 7.20 (d, 1H), 7.13 (t, 2H), 7.01 (d, 2H), 6.90 (t, 1H), 3.35 (bs, 4H), 3.30 (bs, 4H). <sup>13</sup>C NMR (DMSO, 101 MHz) δ 153.3, 137.7, 137.6, 130.8, 129.2, 129.0, 128.9, 127.9, 126.5, 124.9, 124.5, 123.3, 118.7, 113.0, 49.1, 42.8; MS (CI) 368.0 (M + H)<sup>+</sup>, 366.4 (M - H)<sup>-</sup>; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 90%.

#### EXAMPLE 69

##### 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-methoxy-phenyl)-amide, hydrochloride

<sup>1</sup>H NMR (DMSO, 400 MHz) δ 9.59 (s, 1H), 8.76 (d, 1H), 8.23 (d, 1H), 7.93 (d, 1H), 7.64-7.70 (m, 2H), 7.14-7.19 (m, 2H), 7.05 (t, 1H), 6.82 (t, 1H), 6.76 (d, 1H), 3.39 (bs, 4H), 3.29 (bs, 4H), 3.11 (s, 3H). <sup>13</sup>C NMR (DMSO, 101 MHz) δ 152.9, 152.5, 130.6, 129.7, 129.3, 127.9, 127.3, 126.5, 126.3, 125.7, 125.3, 125.2, 124.1, 120.2, 112.8, 111.6, 54.9, 49.2, 43.0. MS (CI) 398.2 (M + H)<sup>+</sup>, 396.2 (M - H)<sup>-</sup>; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 96%.

#### EXAMPLE 70

##### 4-(*cis*-3,5-Dimethyl-piperazin-1-yl)-naphthalene-1-sulfonic acid (2-methoxy-phenyl)-amide, hydrochloride

<sup>1</sup>H NMR (DMSO, 400 MHz) δ 9.75-9.81 (m, 1H), 9.60 (s, 1H), 9.03-9.12 (m, 1H), 8.76 (d, 1H), 8.23 (d, 1H), 7.93 (d, 1H), 7.64-7.71 (m, 2H), 7.05 (t, 1H), 6.82 (t, 1H), 6.76 (d, 1H), 3.63-3.71 (m, 2H), 3.47 (d, 2H), 3.13 (s, 3H), 2.89 (t, 2H), 1.32 (d, 6H). <sup>13</sup>C NMR (DMSO, 101 MHz) δ 152.4, 152.3, 130.6, 129.8, 129.3, 127.9, 127.3, 126.5, 126.3, 125.3,

125.2, 125.1, 124.1, 120.2, 113.0, 111.6, 55.0, 54.9, 51.2, 15.5. MS (CI) 426.2 (M + H)<sup>+</sup>, 424.4 (M - H)<sup>-</sup>; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 96%.

#### EXAMPLE 71

5 4-(*cis*-3,5-Dimethyl-piperazin-1-yl)-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide, hydrochloride

<sup>1</sup>H NMR (MeOD, 400 MHz) δ 8.80 (d, 1H), 8.32 (d, 1H), 8.27 (d, 1H), 7.79 (t, 1H), 7.73 (t, 1H), 7.28 (d, 1H), 7.12 (t, 1H), 7.07 (t, 1H), 6.95-7.00 (m, 2H); MS (CI) 430.2 (M + H)<sup>+</sup>, 428.4 (M - H)<sup>-</sup>; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 98%.

10

#### EXAMPLE 72

4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide, hydrochloride

15 <sup>1</sup>H NMR (MeOD, 400 MHz) δ 8.69 (d, 1H), 8.28 (d, 1H), 8.14 (d, 1H), 7.68 (t, 1H), 7.61 (t, 1H), 7.22 (d, 1H), 7.02 (t, 1H), 6.97 (bs, 1H), 6.86-6.89 (m, 2H), 3.57 (bs, 2H), 3.48 (bs, 4H), 3.33-3.37 (m, 2H), 2.20-2.24 (m, 2H); MS (CI) 416.0 (M + H)<sup>+</sup>, 414.2 (M - H)<sup>-</sup>; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 88%.

#### EXAMPLE 73

20 4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid phenylamide, hydrochloride

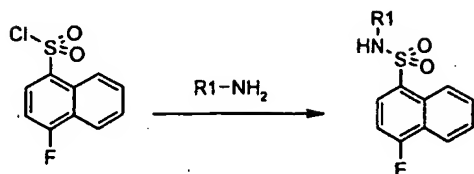
<sup>1</sup>H NMR (MeOD, 400 MHz) δ 8.57 (d, 1H), 8.13 (d, 1H), 7.96 (d, 1H), 7.44-7.55 (m, 2H), 7.04 (d, 1H), 6.90 (t, 2H), 6.72-6.82 (m, 3H), 3.39-3.43 (m, 2H), 3.32-3.36 (m, 4H), 3.17-3.21 (m, 2H), 2.05-2.10 (m, 2H); MS (CI) 382.2 (M + H)<sup>+</sup>, 380.4 (M - H)<sup>-</sup>; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 94%.

25

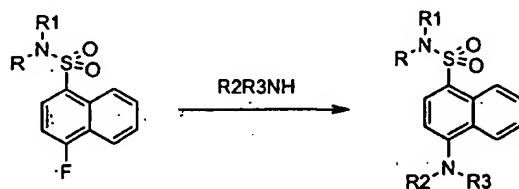
#### EXAMPLE 74

4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide, hydrochloride

30 <sup>1</sup>H NMR (MeOD, 400 MHz) δ 8.69 (d, 1H), 8.23 (d, 1H), 8.16 (d, 1H), 7.68 (t, 1H), 7.62 (t, 1H), 7.17 (d, 1H), 7.02 (t, 1H), 6.97 (t, 1H), 6.85-6.89 (m, 2H), 3.46-3.50 (m, 4H), 3.33 (bs, 4H); MS (CI) 402.2 (M + H)<sup>+</sup>, 400.0 (M - H)<sup>-</sup>; Purity (HPLC, Hichrom 200x4.6 mm I.D.) 98%.

**General method E**

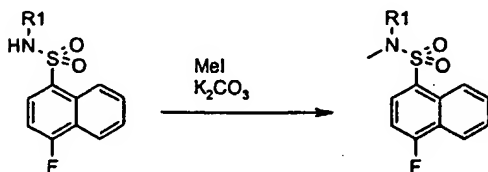
4-Fluoro-naphthalene-1-sulfonylchloride was dissolved in DCM. The amine (1.2eq)  
 5 was added followed by pyridine (3eq). The mixture was stirred for 2h at ambient  
 temperature, diluted with DCM and washed 2 times with HCl (1M). The organic layer was  
 filtered through a silica plug to afford the sulfonamide.

**General method F**

10

The sulfonamide and the amine (5 eq) were dissolved in DMSO and stirred at 100°C  
 overnight. The DMSO solution was added dropwise to water to give a precipitate. After  
 centrifugation, the solvent was decanted and the procedure was repeated. The residue was  
 dissolved in MeOH and converted to HCl salt by adding HCl in ether (2 M) and evaporation.

15

**General method G**

To a solution of the sulfonamide in acetone, K<sub>2</sub>CO<sub>3</sub> (3 eq) was added followed by  
 MeI (1.2 eq). The mixture was stirred overnight, filtered through a short silica plug and  
 20 evaporated to give the methylated sulfonamide.

## EXAMPLE 75

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-methylsulfanyl-phenyl)-amide, hydrochloride**

*N*-(2-methylsulfanyl-phenyl)-4-fluorosulfonamide - Method E; Yield (84 %)

5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.74-8.70 (m, 1 H), 8.29-8.24 (m, 1 H), 8.17-8.14 (m, 1 H), 8.01 (br. s, 1 H), 7.75-7.60 (m, 2 H), 7.50-7.47 (m, 1 H), 7.29-7.25 (m, 1 H), 7.18-7.10 (m, 2 H), 6.98-6.92 (m, 1 H), 2.02 (s, 3 H); MS (ESI+) for  $\text{C}_{17}\text{H}_{14}\text{FN}_2\text{SO}_2$   $m/z$  348 ( $\text{M}+\text{H}$ ) $^+$ .

The final product was prepared according to Method F; Yield 0.77g (53%)

10  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  11.13 (s, 1 H), 9.42 (br. s, 2 H), 8.69-8.66 (m, 1 H), 8.21-8.18 (m, 2 H), 7.76-7.62 (m, 2 H), 7.42-7.21 (m, 5 H), 3.421-3.30 (m, 8 H); MS (ESI+) for  $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$   $m/z$  414.2 ( $\text{M}+\text{H}$ ) $^+$ .

## EXAMPLE 76

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid methyl-naphthalen-1-yl-amide, hydrochloride**

*N*-(1-naphthyl)-4-fluoronaphthalensulfonamide - Method E; Yield (83%)

15  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.77-8.74 (m, 1 H), 8.18-8.05 (m, 2 H), 7.75-7.61 (m, 5 H), 7.41-7.35 (m, 1 H), 7.30-7.26 (m, 1 H), 7.14-7.00 (m, 2 H), 6.93 (br. s, 1 H); MS (ESI+) for  $\text{C}_{20}\text{H}_{14}\text{FN}_2\text{SO}_2$   $m/z$  352 ( $\text{M}+\text{H}$ ) $^+$ .

20 *4-Fluoro-1-naphthalene-1-sulfonic acid methyl-naphthalen-1-yl-amide* - Methylation according to Method G, Yield (97%)

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  8.38-8.35 (m, 1 H), 8.23-8.20 (m, 1 H), 8.16 (dd,  $J = 8.4, 5.5$  Hz, 1 H), 7.99-7.91 (m, 3 H), 7.79-7.73 (m, 1 H), 7.66-7.46 (m, 4 H), 7.37-7.31 (m, 1 H), 7.03 (dd,  $J = 7.5, 1.2$  Hz, 1 H), 3.29 (s, 3 H)

25 The final product was prepared according to Method F; Yield (36%)

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  9.33 (br. s, 1H), 8.40 (d,  $J = 8.4$  Hz, 1 H), 8.25 (d,  $J = 7.9$  Hz, 1 H), 8.09 (d,  $J = 8.2$  Hz, 1 H), 7.98-7.91 (m, 3 H), 7.68-7.62 (m, 1 H), 7.58-7.43 (m, 3 H), 7.40-7.34 (m, 1 H), 7.24 (d,  $J = 8.2$  Hz, 1 H), 7.13-7.10 (m, 1 H), 3.44-3.39 (m, 4 H), 3.29 (br. s, 4 H), 3.25 (s, 3 H); MS (ESI+) for  $\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_2\text{S}$   $m/z$  432 ( $\text{M}+\text{H}$ ) $^+$ .

30

## EXAMPLE 77

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2,3-dihydro-benzo[1,4]dioxin-6-yl)-methyl-amide, hydrochloride**

*N*-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-4-sulfonamide - Method E; Yield (96%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.66-8.63 (m, 1 H), 8.22-8.09 (m, 2 H), 7.77-7.63 (m, 2 H), 7.10 (dd, *J* = 8.2, 9.5 Hz, 1 H), 6.58 (d, *J* = 8.5 Hz, 1 H), 6.46 (d, *J* = 2.4 Hz, 1 H), 6.30 (dd, *J* = 2.6, 8.7 Hz, 1 H), 4.14 (s, 4 H); MS (ESI+) for C<sub>18</sub> H<sub>14</sub> F N O<sub>4</sub> S *m/z* 360 (M+H)<sup>+</sup>.

*4-Fluoro-Nl-naphthalene-1-sulfonic acid* -(2,3-dihydro-benzo[1,4]dioxin-6-yl)-methyl-amide - Methylation according to Method G; Yield (100%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.19-8.13 (m, 2 H), 8.09 (dd, *J* = 8.4, 5.5 Hz, 1 H), 7.75-7.70 (m, 1 H), 7.64-7.58 (m, 1 H), 7.50 (dd, *J* = 10.0, 8.4 Hz, 1 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 6.55 (d, *J* = 2.6 Hz, 1 H), 6.51-6.47 (m, 1 H), 4.20-4.15 (m, 4 H), 3.10 (s, 3 H)

The final product was prepared according to Method F; the product precipitates in MeOH; Yield (57%): <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.29 (br. s, 2 H), 8.23-8.16 (m, 2 H), 8.01 (d, *J* = 8.2 Hz, 1 H), 7.64-7.49 (m, 2 H), 7.25 (d, *J* = 8.2 Hz, 1 H), 6.72 (d, *J* = 8.4 Hz, 1 H), 6.56-6.48 (m, 2 H), 4.21-4.16 (m, 4 H), 3.38-3.31 (m, 4 H), 3.08 (s, 3 H); MS (ESI+) for C<sub>23</sub> H<sub>25</sub> N<sub>3</sub> O<sub>4</sub> S *m/z* 440 (M+H)<sup>+</sup>.

**EXAMPLE 78**

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2,3-dihydro-benzo[1,4]dioxin-6-yl)-amide, hydrochloride**

The final product was prepared according to Method F; Yield (36%); <sup>1</sup>H NMR (270 MHz, DMSO-D<sub>6</sub>) δ ppm 3.32 (m, 8 H) 4.08 (m, 4 H) 6.45 (m, 2 H) 6.61 (d, *J*=8.44 Hz, 1 H) 7.20 (d, *J*=8.18 Hz, 1 H) 7.67 (m, 2 H) 8.07 (d, *J*=7.92 Hz, 1 H) 8.21 (d, *J*=8.71 Hz, 1 H) 8.67 (d, *J*=8.44 Hz, 1 H) 9.22 (s, 1 H) 10.32 (s, 1 H); MS (ESI+) for C<sub>22</sub> H<sub>23</sub> N<sub>3</sub> O<sub>4</sub> S *m/z* 426.2 (M+H)<sup>+</sup>.

**EXAMPLE 79**

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid methyl-(2-methylsulfanyl-phenyl)-amide, hydrochloride**

*4-Fluoro-N-methyl-N*-(2-methylsulfanyl-phenyl)-amide - Methylation according to Method G; Yield (97%); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.52-8.49 (m, 1 H), 8.22-8.19 (m, 1 H), 8.16

(dd,  $J = 8.4, 5.5$  Hz, 1 H), 7.79-7.66 (m, 2 H), 7.52 (dd,  $J = 10.0, 8.4$  Hz, 1 H), 7.37-7.24 (m, 2 H), 7.06-7.00 (m, 1 H), 6.88 (dd,  $J = 7.9, 1.3$  Hz, 1 H), 3.10 (s, 3 H), 2.28 (s, 3 H).

The final product was prepared according to Method F; Trituration with MeCN; Yield (65%)

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  9.27 (br. s, 2 H), 8.54-8.50 (m, 1 H), 8.27-8.23 (m, 1 H), 8.09 (d,  $J =$   
5 8.2 Hz, 1 H), 7.67-7.56 (m, 2 H), 7.38-7.25 (m, 3 H), 7.07-6.92 (m, 2 H), 3.41-3.33 (m, 8 H),  
3.06 (s, 3 H), 2.30 (s, 3 H); MS (ESI+) for C<sub>22</sub> H<sub>25</sub> N<sub>3</sub> O<sub>2</sub> S<sub>2</sub>  $m/z$  428 (M+H)<sup>+</sup>.

#### EXAMPLE 80

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid methyl-(3-trifluoromethyl-phenyl)-amide,**  
10 **hydrochloride**

*N*-(3-trifluoromethylphenyl)-4-fluoronaphthalenesulfonamide - Method E; Yield  
(90%).  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  8.65-8.62 (m, 1 H), 8.23-8.18 (m, 2 H), 7.78-7.65 (m, 2 H), 7.31-  
7.17 (m, 2 H), 7.16-7.08 (m, 3 H); MS (ESI+) for C<sub>17</sub> H<sub>11</sub> F<sub>4</sub> N O<sub>2</sub> S  $m/z$  370 (M+H)<sup>+</sup>.

Methylation according to Method F; Yield (100%);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  8.19-8.11 (m, 2  
15 H), 8.01-7.98 (m, 1 H), 7.73-7.62 (m, 2 H), 7.57-7.44 (m, 4 H), 7.35 (br. s, 1 H), 3.21 (s, 3  
H).

The final product was prepared according to Method F; Trituration with MeCN; Yield  
0.07g (40%).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  9.35 (br. s, 2 H), 8.21 (d,  $J = 8.2$  Hz, 1 H), 8.06-8.02  
(m, 2 H), 7.63-7.42 (m, 5 H), 7.28-7.24 (m, 2 H), 3.39 (br. s, 8 H), 3.21 (s, 3 H), 2.06 (s, 3  
20 H); MS (ESI+) for C<sub>22</sub> H<sub>22</sub> F<sub>3</sub> N<sub>3</sub> O<sub>2</sub> S  $m/z$  450 (M+H)<sup>+</sup>.

#### EXAMPLE 81

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-chloro-4-methyl-phenyl)-methyl-amide,**  
25 **hydrochloride**

*N*-(3-Chloro-4-methylphenyl)-4-fluoronaphthalenesulfonamide - Method E; Yield  
(88%).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  10.86 (br. s, 1 H), 8.74-8.71 (m, 1 H), 8.22 (dd,  $J = 8.3, 5.4$   
Hz, 1 H), 8.19-8.16 (m, 1 H), 7.89-7.75 (m, 2 H), 7.47 (dd,  $J = 10.0, 8.4$  Hz, 1 H), 7.12-7.09  
(m, 1 H), 7.00 (d,  $J = 2.2$  Hz, 1 H), 6.86 (dd,  $J = 8.3, 2.2$  Hz, 1 H), 2.11 (s, 3 H);

30 *4-Fluoro-1-naphthalene-1-sulfonic acid (3-chloro-4-methyl-phenyl)-methyl-amide* -  
Methylation according to Method G; Yield (100%).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  8.20-8.07 (m, 3

H), 7.76-7.70 (m, 1 H), 7.62-7.48 (m, 2 H), 7.27-7.24 (m, 1 H), 7.13 (d,  $J = 2.4$  Hz, 1 H), 6.99 (dd,  $J = 8.2, 2.4$  Hz, 1 H), 3.15 (s, 3 H), 2.28 (s, 3 H);

The final product was prepared according to Method F; Yield (28%).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  9.29 (br. s, 2 H), 8.24-8.15 (m, 2 H), 8.01 (d,  $J = 8.2$  Hz, 1 H), 7.65-7.47 (m, 2 H), 7.26 (dd,  $J = 8.3, 4.6$  Hz, 2 H), 7.09-7.08 (1 H), 7.03-6.99 (m, 1H), 3.38-3.33 (m, 8 H), 3.14 (s, 3 H), 2.27 (s, 3 H); MS (ESI+) for C<sub>22</sub> H<sub>24</sub> Cl N<sub>3</sub> O<sub>2</sub> S  $m/z$  430 (M+H)<sup>+</sup>.

#### EXAMPLE 82

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-ethyl-phenyl)-methyl-amide,**

**hydrochloride**

*N*-(3-ethylphenyl)-4-fluoronaphthalenesulfonamide - Method E; Yield (85%).

$^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  8.66 (d,  $J = 8.4$  Hz, 1 H), 8.20-8.14 (m, 2 H), 7.75-7.62 (m, 2 H), 7.10 (dd,  $J = 9.5, 8.4$  Hz, 1 H), 7.02 (t,  $J = 7.8$  Hz, 1 H), 6.88-6.85 (m, 1 H), 6.72-6.68 (m, 3 H), 2.45 (q,  $J = 7.7$  Hz, 2 H), 1.03 (t,  $J = 7.7$  Hz, 3 H)

*4-Fluoro-1-yl-naphthalene-1-sulfonic acid (3-ethyl-phenyl)-methyl-amide -*

Methylation according to Method G; Yield (100%);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  8.18-8.06 (m, 3 H), 7.72-7.66 (m, 1 H), 7.54-7.48 (m, 2 H), 7.21-7.16 (m, 1 H), 7.10-7.08 (m, 1 H), 6.96-6.92 (m, 1 H), 6.81-6.80 (m, 1 H), 3.16 (s, 3 H), 2.41 (q,  $J = 7.5$  Hz, 2 H), 0.93 (t,  $J = 7.5$  Hz, 3 H)

The final product was prepared according to Method f; Trituration with MeCN; Yield (49%);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  9.21 (br. s, 2 H), 8.21 (d,  $J = 8.4$  Hz, 1 H), 8.13 (d,  $J = 8.7$  Hz, 1 H), 8.02 (d,  $J = 8.2$  Hz, 1 H), 7.62-7.57 (m, 1 H), 7.47-7.41 (m, 1 H), 7.27-7.17 (m, 2 H), 7.10-6.95 (m, 2 H), 6.8 (br. s, 1 H), 3.40-3.29 (m, 8 H), 3.15 (s, 3 H), 2.43 (q,  $J = 7.6$  Hz, 2 H), 0.95 (t,  $J = 7.6$  Hz, 2 H); MS (ESI+) for C<sub>23</sub> H<sub>27</sub> N<sub>3</sub> O<sub>2</sub> S  $m/z$  410 (M+H)<sup>+</sup>.

#### EXAMPLE 83

**4-(3,5-Dimethyl-piperazin-1-yl)-naphthalene-1-sulfonic acid (2-isopropyl-phenyl)-amide, hydrochloride**

The final product was prepared according to Method F; Yield (35%);  $^1\text{H}$  NMR (270 MHz, DMSO-D<sub>6</sub>)  $\delta$  ppm 0.64 (d,  $J = 6.86$  Hz, 6 H) 1.30 (d,  $J = 6.60$  Hz, 6 H) 2.92 (m, 3 H) 3.53 (m, 4 H) 6.86 (d,  $J = 7.65$  Hz, 1 H) 6.98 (m, 1 H) 7.13 (m, 3 H) 7.67 (m, 2 H) 7.86 (d,



$J=7.92$  Hz, 1 H) 8.24 (m, 1 H) 8.74 (m, 1 H) 9.08 (m, 1 H) 9.79 (m, 2 H); MS (ESI+) for C<sub>25</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>S  $m/z$  438.01 (M+H)<sup>+</sup>.

#### EXAMPLE 84

5    **4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (2-isopropyl-phenyl)-amide, hydrochloride**

*N*-(2 isopropylphenyl)-4-fluoronaphthalensulfonamide - Method E; Yield (87%)

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.67-8.64 (m, 1 H), 8.22-8.18 (m, 1 H), 8.12 (dd,  $J=8.3, 5.4$  Hz, 1 H), 7.71-7.62 (m, 2 H), 7.15-6.97 (m, 5 H), 2.84-2.73 (m, 1 H), 0.85 (s, 3 H), 0.82 (s, 3 H)

10    The final product was prepared according to Method F; Yield (22%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.83 (s, 1 H), 9.37 (br. s, 2 H), 8.74-8.70 (m, 1 H), 8.27-8.24 (m, 1 H), 7.84 (d,  $J=7.9$  Hz, 1 H), 7.68-7.64 (m, 2 H), 7.17-7.11 (m, 3 H), 7.01-6.87 (m, 2 H), 3.82 (br. s, 6 H), 3.51-3.50 (m, 2 H), 3.38-3.28 (m, 2 H), 3.02-2.93 (m, 1 H), 0.65 (s, 3 H), 0.63 (s, 3 H); MS (ESI+) for C<sub>24</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>S  $m/z$  424.02 (M+H)<sup>+</sup>.

15

#### EXAMPLE 85

**4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-ethyl-phenyl)-amide, hydrochloride**

The final product was prepared according to Method F; Yield (22%); <sup>1</sup>H NMR

(DMSO-*d*<sub>6</sub>) δ 10.53 (s, 1 H), 9.24 (br. s, 2 H), 8.68 (d,  $J=8.2$  Hz, 1 H), 8.20 (d,  $J=7.9$  Hz, 1 H), 8.14 (d,  $J=8.2$  Hz, 1 H), 7.72-7.60 (m, 2 H), 7.22 (d,  $J=8.2$  Hz, 1 H), 7.01 (t,  $J=7.8$  Hz, 1 H), 6.83-6.72 (m, 3 H), 3.33 (br. s, 6 H), 2.39 (q,  $J=7.7$  Hz, 2 H), 2.12 (br. s, 2 H), 0.98 (t,  $J=7.5$  Hz, 3 H); MS (ESI+) for C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S  $m/z$  410.03 (M+H)<sup>+</sup>.

20

#### EXAMPLE 86

25    **N-(2-Fluorophenyl)-4-piperazin-1-yl-naphthalene-1-sulfonamide, hydrochloride**

*N*-(2-Fluorophenyl)-4-fluoronaphthalensulfonamide - Method E; Yield (88%); <sup>1</sup>H

NMR (DMSO-*d*<sub>6</sub>) δ 10.41 (br. s, 1 H), 8.76-8.69 (m, 1 H), 8.20-8.17 (m, 1 H), 8.08 (dd,  $J=8.0, 5.5$  Hz, 1 H), 7.82-7.75 (m, 2 H), 7.41 (dd,  $J=10.0, 8.3$  Hz, 1 H), 7.20-7.01 (m, 4 H); MS (ESI-) for C<sub>16</sub>H<sub>11</sub>F<sub>2</sub>N<sub>3</sub>O<sub>2</sub>S  $m/z$  318.2 (M-H)<sup>-</sup>.

The final product was prepared according to Method F; Yield (22%); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.41 (s, 1 H), 9.35 (m, 2 H), 8.72-8.68 (m, 1 H), 8.24-8.20 (m, 1 H), 8.02 (d, *J* = 7.9 Hz, 1 H), 7.72-7.62 (m, 2 H), 7.22-7.00 (m, 5 H), 4.05 (d, *J* = 1.3 Hz, 4 H), 3.36 (s, 4 H); MS (ESI+) for C<sub>20</sub> H<sub>20</sub> F N<sub>3</sub> O<sub>2</sub> S *m/z* 386 (M+H)<sup>+</sup>.

5

**EXAMPLE 87**

**4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-trifluoromethyl-phenyl)-amide, hydrochloride**

The final product was prepared according to Method F; Yield (21%); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.1 (s, 1 H), 9.32 (br. s, 2 H), 8.65 (d, *J* = 8.2 Hz, 1 H), 8.19 (t, *J* = 8.6 Hz, 2 H), 7.75-7.62 (m, 2 H), 7.42-7.22 (m, 4 H), 3.88 (br. s, 6 H), 3.55-3.53 (m, 2 H), 2.11 (m, 2 H); MS (ESI+) for C<sub>22</sub> H<sub>22</sub> F<sub>3</sub> N<sub>3</sub> O<sub>2</sub> S *m/z* 449.95 (M+H)<sup>+</sup>.

**EXAMPLE 88**

***N*-(2,4-difluorophenyl)-4-piperazin-1-yl-naphthalene-1-sulfonamide, hydrochloride**

*N*-(2,4-di-Fluorophenyl)-4-fluoronaphthalensulfonamide - Method E; Yield (81%); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.44 (s, 1 H), 8.73-8.69 (m, 1 H), 8.21-8.18 (m, 1 H), 8.02 (dd, *J* = 8.4, 5.5 Hz, 1 H), 7.85-7.76 (m, 2 H), 7.41 (dd, *J* = 10.2, 8.3 Hz, 1 H), 7.22-7.11 (m, 2 H), 7.01-6.93 (m, 1 H); MS (ESI-) for C<sub>16</sub> H<sub>10</sub> F<sub>3</sub> N O<sub>2</sub> S *m/z* 336.2 (M-H)<sup>-</sup>.

The final product was prepared according to Method F; Yield (27%); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.33 (s, 1 H), 9.28 (br. s, 2 H), 8.68-8.65 (m, 1 H), 8.25-8.21 (m, 1 H), 8.0 (d, *J* = 8.2 Hz, 1 H), 7.73-7.62 (m, 2 H), 7.21-7.08 (m, 3 H), 7.0-6.93 (m, 1 H), 3.29 (br. s, 4 H); MS (ESI+) for C<sub>20</sub> H<sub>19</sub> F<sub>2</sub> N<sub>3</sub> O<sub>2</sub> S *m/z* 403.94 (M+H)<sup>+</sup>.

**EXAMPLE 89**

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-trifluoromethoxy-phenyl)-amide, hydrochloride**

*N*-(2-tri-Fluoromethoxyphenyl)-4-fluoronephthylsulfonamide - Method E; Yield (43%); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.58 (s, 1 H), 8.80-8.76 (m, 1 H), 8.20-8.17 (m, 1 H), 8.08 (dd, *J* = 8.3, 5.4 Hz, 1 H), 7.84-7.74 (m, 2 H), 7.42 (dd, *J* = 10.2, 8.3 Hz, 1 H), 7.32-7.18 (m, 4 H).

The final product was prepared according to Method F; Yield (48%); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 10.49 (s, 1 H), 9.27 (br. s, 2 H), 8.75-8.72 (m, 1 H), 8.24-8.21 (m, 1 H), 8.02 (d, J = 7.9 Hz, 1 H), 7.71-7.62 (m, 2 H), 7.32-7.17 (m, 5 H), 3.38 (br. s, 4 H), 3.28 (br. s, 4 H); S (ESI+) for C<sub>21</sub> H<sub>20</sub> F<sub>3</sub> N<sub>3</sub> O<sub>3</sub> S *m/z* 451.9 (M+H)<sup>+</sup>.

5

## EXAMPLE 90

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-phenoxy-phenyl)-amide, hydrochloride***N*-(3-phenoxyphenyl)-4-fluoronaphthylsulfonamide - Method E; Yield 0.64g

(100%); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 10.80 (br. s, 1 H), 8.71-8.68 (m, 1 H), 8.19-8.16 (m, 1 H),  
10 8.10 (dd, J = 8.3, 5.4 Hz, 1 H), 7.85-7.74 (m, 2 H), 7.45 (dd, J = 10.2, 8.3 Hz, 1 H), 7.38-7.31 (m, 2' H), 7.18-7.10 (m, 2 H), 6.82-6.73 (m, 3 H), 6.58-6.55 (m, 2 H); MS (ESI-) for C<sub>22</sub> H<sub>16</sub> F N O<sub>3</sub> S *m/z* 392.2 (M-H)<sup>-</sup>.

The final product was prepared according to Method F; Yield 0.08g (31%); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 10.76 (s, 1 H), 9.37 (br. s, 2 H), 8.67-8.63 (m, 1 H), 8.23-8.20 (m, 1 H), 8.02  
15 (d, J = 8.2 Hz, 1 H), 7.73-7.62 (m, 2 H), 7.41-7.35 (m, 2 H), 7.20-7.09 (m, 3 H), 6.84-6.73 (m, 3 H), 6.60-6.52 (m, 2 H), 3.47-3.37 (m, 8 H); MS (ESI+) for C<sub>26</sub> H<sub>25</sub> N<sub>3</sub> O<sub>3</sub> S *m/z* 459.95 (M+H)<sup>+</sup>.

## EXAMPLE 91

20 **4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-trifluoromethoxy-phenyl)-amide, hydrochloride**

*N*-(3-Trifluoromethoxyphenyl)-4-fluoronaphthalensulfonamide - Method E; Yield

(35%); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 11.01 (br.s, 1 H), 8.74-8.71 (m, 1 H), 8.26 (dd, J = 8.3, 5.3 Hz, 1 H), 8.16 (d, J = 9.0 Hz, 1 H), 7.86-7.82 (m, 1 H), 7.78-7.74 (m, 1 H), 7.46 (dd, J =  
25 10.0, 8.5 Hz, 1 H), 7.27 (t, J = 8.3 Hz, 1 H), 7.02-6.90 (m, 3 H); MS (ESI-) for C<sub>17</sub> H<sub>11</sub> F<sub>4</sub> N O<sub>3</sub> S *m/z* 383.8 (M-H)<sup>-</sup>.

The final product was prepared according to Method F; Yield (35%); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 11.07 (s, 1 H), 9.63 (br. s, 1 H), 9.31 (br. s, 1 H), 8.66 (d, J = 8.4 Hz, 1 H),  
8.21-8.18 (m, 2 H), 7.75-7.62 (m, 2 H), 7.29-7.21 (m, 2 H), 7.03-6.86 (m, 3 H), 3.32-3.28 (m,  
30 8 H); MS (ESI+) for C<sub>26</sub> H<sub>25</sub> N<sub>3</sub> O<sub>3</sub> S *m/z* 451.94 (M+H)<sup>+</sup>.

## EXAMPLE 92

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-chloro-5-methyl-phenyl)-amide, hydrochloride**

The final product was prepared according to method F:  $^1\text{H}$  NMR ((DMSO- $d_6$ )  $\delta$ :  
5 10.10 (brs, 1H), 9.25 (brs, 2H), 8.76-8.66 (m, 1H), 8.27-8.17 (m, 1H), 8.00-7.94 (m, 1H),  
7.71-7.60 (m, 2H), 7.25-7.11 (m, 2H), 7.02 (s, 1H), 6.99-6.92 (m, 1H), 3.40-3.20 (m,  
obscured by solvent signal) 2.17 (s, 3H), MS (posESI)  $m/z$  = 416 (M+H).

## EXAMPLE 93

10 **4-Piperazin-1-yl-naphthalene-1-sulfonic acid (4-isopropyl-phenyl)-amide, hydrochloride**

The final product was prepared according to method F:  $^1\text{H}$  NMR ((DMSO- $d_6$ )  $\delta$ :  
10.52 (s, 1H), 9.26 (brs, 2H), 8.74-8.66 (m, 1H), 8.27-8.11 (m, 2H), 7.76-7.60 (m, 2H),  
7.26-7.17 (m, 1H), 7.06-6.89 (m, 4H), 3.40-3.20 (m, obscured by solvent signal), 2.77-2.61  
(m, 1H), 1.05 (d,  $J$  = 6.87 Hz, 6H), MS (posESI)  $m/z$  = 410 (M+H).

15

## EXAMPLE 94

***N*-(3,5-Difluorophenyl)-4-piperazin-1-yl-naphthalene-1-sulfonamide, hydrochloride**

The final product was prepared according to Method F using the crude *N*-(3,5-  
difluorophenyl)-4-fluoronaphthalene-1-sulfonamide (50 mg, 0.15 mmol) afforded the title  
20 compound (20 mg, 31%) as a yellow solid.  $^1\text{H}$  NMR (DMSO)  $\delta$  11.33 (s, 1H), 9.35 (br s,  
2H), 8.69 (m, 1H), 8.30-8.18 (m, 2H), 7.80-7.61 (m, 2H), 7.30-7.21 (m, 1H), 6.84-6.62 (m,  
3H), 3.45-3.24 (m, 8H); MS  $m/z$  (M+1) 404.

## EXAMPLE 95

25 **1-[4-(3,4-Dihydroquinolin-1(2H)-ylsulfonyl)-1-naphthyl]piperazine, hydrochloride**

*4-Fluoronaphthalene-1-sulfonyl chloride* - To a stirred solution of 1-fluoronaphthalene (8.0 g, 55 mmol) in concentrated trifluoroacetic acid (40 ml), chlorosulfonic acid was added slowly (15 min) at 0°C. The mixture was stirred at room temperature for an additional 2 hours and then added slowly onto a stirred ice slurry. The  
5 formed precipitate filtered off, washed with cold water and dried in vacuo to give the title compound (7.3 g) as a white solid.

*1-[(4-Fluoro-1-naphthyl)sulfonyl]-1,2,3,4-tetrahydroquinoline* – Method E: To a stirred solution of 4-fluoronaphthalene-1-sulfonyl chloride (200mg, 0.82 mmol) in DCM (1 ml) was added 1,2,3,4-tetrahydroquinoline (123  $\mu$ l, 0.98 mmol) followed by pyridine (0.25  
10 ml). The reaction mixture was stirred over night, diluted with DCM and washed with 1M HCl (3x3 ml). Subsequent drying of the organic phase using MgSO<sub>4</sub>, and removal of the solvents in vacuo afforded the title compound (280 mg, 100%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.24-8.10 (m, 3H), 7.68-7.62 (m, 1H), 7.58-7.51 (m, 1H), 7.42-7.34 (m, 1H), 7.23-7.04 (m, 3H), 6.96-6.89 (m, 1H), 3.84-3.74 (m, 2H), 2.39-2.28 (m, 2H), 1.63-1.49 (m, 1H);  
15 MS m/z (M+1) 342.

The final product was prepared according to Method F: A stirred solution of 1-[(4-fluoro-1-naphthyl)sulfonyl]-1,2,3,4-tetrahydroquinoline (50 mg, 0.15 mmol) and piperazine (80 mg, 0.9 mmol) in DMSO (1 ml) was heated at 95°C over night. The reaction mixture was allowed to reach room temperature and was subsequently added dropwise into water. The  
20 formed solid was isolated, re-dissolved in MeOH and treated with an excess of 1M HCl in diethyl ether. Removal of the solvents in vacuo afforded the title compound (60 mg, 83%) as a white solid. <sup>1</sup>H NMR (DMSO)  $\delta$  9.17 (br s, 2H), 8.23-8.06 (m, 3H), 7.61-7.55 (m, 1H), 7.48-7.38 (m, 2H), 7.29-7.23 (m, 1H), 7.19-7.12 (m, 1H), 7.09-6.98 (m, 2H), 3.78-3.71 (m, 2H), 3.44-3.30 (m, 8H), 2.42-2.32 (m, 2H), 1.57-1.48 (m, 2H); MS m/z (M+1) 408.

25

#### EXAMPLE 96

##### **4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-nitro-phenyl)-amide, hydrochloride**

The final product was prepared according to Method F: <sup>1</sup>H NMR ((DMSO-*d*<sub>6</sub>)  $\delta$ ; 8.68-8.63 (m, 1H), 8.27-8.13 (m, 2H), 7.78 (s, 1H), 7.72-7.53 (m, 3H), 7.35-7.16 (m, 3H),  
30 3.55-3.40 (m, 6H), 3.34-3.27 (m, obscured in part by solvent signal), 2.22-2.13 (m, 2H), MS (posESI) m/z = 427 (M+H).

## EXAMPLE 97

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-nitro-phenyl)-amide, hydrochloride**

The final product was prepared according to Method F:  $^1\text{H}$  NMR ((DMSO- $d_6$ )  $\delta$ ; 8.68-8.60 (m, 1H), 8.24-8.13 (m, 2H), 7.77 (s, 1H), 7.71-7.53 (m, 3H), 7.30-7.20 (m, 2H), 7.16-7.10 (m, 1H), 3.45-3.40 (m, 4H), 3.31-3.20 (m, 4H), MS (posESI)  $m/z = 413$  (M+H).

## EXAMPLE 98

**4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-nitro-phenyl)-methyl-amide, hydrochloride**

The final product was prepared according to Method F:  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ ; 8.21 (d,  $J = 8.47$  Hz, 1H), 8.12 (d,  $J = 8.79$  Hz, 1H), 8.01-7.95 (m, 2H), 7.64 (s, 1H), 7.54-7.39 (m, 3H), 7.34-7.28 (m, 1H), 7.23-7.18 (m, 1H), 3.60-3.30 (m, 8H), 3.17 (s, 3H), 2.24-2.16 (m, 2H), MS (posESI)  $m/z = 441$  (M+H).

## EXAMPLE 99

**N-(4-Methylphenyl)-4-piperazin-1-yl-naphthalene-1-sulfonamide, hydrochloride**

*4-Fluoro-N-(4-methylphenyl)naphthalene-1-sulfonamide* – Method E: Use of 4-methylaniline afforded the title compound (500 mg, 95%) as an oil by the application of the general procedure A described above.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.82-8.75 (m, 1H), 8.22-8.13 (m, 2H), 7.73-7.58 (m, 2H), 7.44 (s, 1H), 7.11-7.02 (m, 1H), 6.93-6.80 (m, 4H), 2.17 (s, 3H); MS  $m/z$  (M+1) 316.

The final product was prepared according to Method E: Use of 4-fluoro-N-(4-methylphenyl)naphthalene-1-sulfonamide afforded the title compound (200 mg, 30%), after washing with methanol, as a yellow solid.  $^1\text{H}$  NMR (DMSO)  $\delta$  10.46 (s, 1H), 9.30 (br s, 2H), 8.76-8.65 (m, 1H), 8.25-8.06 (m, 2H), 7.78-7.59 (m, 2H), 7.25-7.14 (m, 1H), 6.98-6.83 (4H), 3.41-3.22 (m, 8H), 2.09 (s, 3H); MS  $m/z$  (M+1) 382.

## EXAMPLE 100

**N-(3-Chloro-4-methylphenyl)-4-piperazin-1-yl-naphthalene-1-sulfonamide, hydrochloride**

The final product was prepared according to Method E: yield 100%, purity 93%  
<sup>1</sup>H NMR (500 MHz, DMSO-D<sub>6</sub>) δ ppm 2.26 (s, 3 H), 2.74 (m, 4 H), 3.54 (m, 4 H), 7.23 (m, 4 H), 7.83 (m, 2 H), 8.31 (m, 2 H), 8.81 (s, 1 H), 9.11 (s, 1 H, N-H), 10.86 (s, 1 H, N-H); MS (ESI+) for C<sub>21</sub> H<sub>22</sub> Cl N<sub>3</sub> O<sub>2</sub> S HCl *m/z* (M+H)<sup>+</sup>. 416.1; MS (ESI-) for C<sub>21</sub> H<sub>22</sub> Cl N<sub>3</sub> O<sub>2</sub> S HCl *m/z* (M-H)<sup>-</sup>. 414.1.

#### EXAMPLE 101

##### 4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (2,3-dimethyl-phenyl)-methyl-amide, hydrochloride

The final product was prepared according to Method F: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 8.51-8.41 (m, 1H), 8.39-8.30 (m, 1H), 8.11-7.99 (m, 1H), 7.68-7.56 (m, 1H), 7.54-7.42 (m, 1H), 7.35-7.23 (m, 1H), 7.13-7.02 (M, 1H), 6.90-6.78 (m, 1H), 6.62-6.47 (m, 1H), 3.70-3.40 (m, 8H), 3.17 (s, 3H), 2.25 (s, 3H), 2.10 (s, 3H), MS (posESI) *m/z* = 424 (M+H).

#### EXAMPLE 102

##### 4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (4-isopropyl-phenyl)-amide, hydrochloride

The final product was prepared according to Method F: <sup>1</sup>H NMR ((DMSO-*d*<sub>6</sub>) δ; 8.74 (d, J = 8.16 Hz, 1H), 8.33 (d, J = 8.48 Hz, 1H), 8.15-8.10 (m, 1H), 7.72-7.62 (m, 2H), 7.25-7.21 (m, 1H), 6.99-6.86 (m, 4H), 3.62-3.57 (m, 2H), 3.56-3.50 (m, 4H), 3.41-3.35 (m, 2H), 2.79-2.69 (m, 1H), 2.32-2.22 (m, 2H), 1.14-1.10 (m, 6H), MS (posESI) *m/z* = 424 (M+H).

#### EXAMPLE 103

##### 4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (4-isopropyl-phenyl)-methyl-amide, hydrochloride

The final product was prepared according to Method F: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 8.13-8.07 (m, 1H), 8.01-7.93 (m, 1H), 7.51-7.41 (m, 1H), 7.38-7.15 (m, 2H), 7.00-6.95 (m, 2H), 6.89-6.85 (m, 2H), 3.59-3.28 (m, 8H), 3.09 (s, 3H), 2.81-2.71 (m, 1H), 1.11 (d, J = 6.60 Hz, 6H), MS (posESI) *m/z* = 438 (M+H).

## EXAMPLE 104

**4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (2,4-dimethyl-phenyl)-amide, hydrochloride**

The final product was prepared according to Method F:  $^1\text{H}$  NMR ((DMSO- $d_6$ )  $\delta$ ;  
5 8.70-8.61 (m, 1H), 8.30-8.20 (m, 1H), 7.91-7.78 (m, 1H), 7.60-7.51 (m, 2H), 7.14-7.06 (m, 1H), 6.76-6.59 (m, 3H), 3.64-3.40 (m, 6H), 3.35-3.30 (m, obscured in part by solvent signal), 2.24-2.13 (m, 2H), 2.07 (s, 3H), 1.76 (s, 3H), MS (posESI)  $m/z$  = 410 (M+H).

## EXAMPLE 105

**4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (2-chloro-5-methyl-phenyl)-amide, hydrochloride**

The final product was prepared according to Method F:  $^1\text{H}$  NMR ((DMSO- $d_6$ )  $\delta$ ;  
8.67-8.61 (m, 1H), 8.24-8.19 (m, 1H), 7.95 (d,  $J$  = 8.16 Hz, 1H), 7.57-7.56 (m, 2H), 7.21-7.18 (m, 1H), 7.12 (d,  $J$  = 8.17 Hz, 1H), 6.89 (d,  $J$  = 8.17 Hz, 1H), 6.78-6.75 (m, 1H), 3.52-  
15 3.47 (m, 2H), 3.45-3.40 (m, 4H), 3.31-3.26 (m, 2H), 2.20-2.10 (m, 2H), 2.14 (s, 3H), MS (posESI)  $m/z$  = 430 (M+H).

## EXAMPLE 106

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2,5-dimethoxy-phenyl)-amide, hydrochloride**

The final product was prepared according to Method F:  $^1\text{H}$  NMR ((DMSO- $d_6$ )  $\delta$ ;  
8.80-8.72 (m, 1H), 8.27-8.19 (m, 1H), 7.98 (d,  $J$  = 8.18 Hz, 1H), 7.74-7.60 (m, 2H), 7.17 (d,  $J$  = 7.91 Hz, 1H), 6.76-6.75 (m, 2H), 6.62-6.55 (m, 1H), 3.60 (s, 3H), 3.40-3.20 (m, obscured by solvent signal), 3.12 (s, 3H), MS (posESI)  $m/z$  = 428 (M+H).

## EXAMPLE 107

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-acetyl-phenyl)-amide; hydrochloride**

The final product was prepared according to Method F:  $^1\text{H}$  NMR ((DMSO- $d_6$ )  $\delta$ ;  
8.79-8.72 (m, 1H), 8.29-8.21 (m, 2H), 7.75-7.62 (m, 2H), 7.59-7.52 (m, 2H), 7.26-7.19 (m, 3H), 3.52-3.44 (m, 4H), 3.39-3.30 (m, obscured by solvent signal), 2.43 (s, 3H), MS (posESI)  
30  $m/z$  = 410 (M+H).



## EXAMPLE 108

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2,4-dimethyl-phenyl)-amide, hydrochloride**

5       The final product was prepared according to Method F:  $^1\text{H}$  NMR ((DMSO- $d_6$ )  $\delta$ : 8.81-8.72 (m, 1H), 8.34-8.25 (m, 1H), 7.98 (d,  $J$  = 8.18 Hz, 1H), 7.71-7.60 (m, 2H), 7.14 (d,  $J$  = 8.18 Hz, 1H), 6.81 (s, 1H), 6.76-6.72 (m, 2H), 3.58-3.47 (m, 4H), 3.44-3.30 (m, obscured in part by solvent signal), 2.16 (s, 3H), 1.84 (s, 3H), MS (posESI)  $m/z$  = 396 (M+H).

## 10   EXAMPLE 109

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-trifluoromethyl-phenyl)-amide, hydrochloride**

      The final product was prepared according to Method F:  $^1\text{H}$  NMR ((DMSO- $d_6$ )  $\delta$ : 8.72-8.64 (m, 1H), 8.27-8.16 (m, 2H), 7.81-7.62 (m, 2H), 7.45-7.19 (m, 5H), 3.40-3.20 (m, 15 obscured by solvent signal), MS (posESI)  $m/z$  = 436 (M+H).

## EXAMPLE 110

**4-Piperazin-1-yl-naphthalene-1-sulfonic acid biphenyl-2-ylamide, hydrochloride**

      The final product was prepared according to Method F:  $^1\text{H}$  NMR ((DMSO- $d_6$ )  $\delta$ : 9.71 (s, 1H), 9.44 (brs, 2H), 8.51-8.42 (m, 1H), 8.24-8.15 (m, 1H), 7.83 (d,  $J$  = 8.18 Hz, 1H), 20 7.66-7.49 (m, 2H), 7.29-6.98 (m, 10H), 3.50-3.30 (m, obscured by solvent signal), MS (posESI)  $m/z$  = 444 (M+H).

## EXAMPLE 111

25   **4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-benzyloxy-phenyl)-amide,**

*N*-(3-phenyloxyphenyl)-4-fluoronaphthalensulfonamide - Method E; Yield 9.2g (47%).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  10.75 (s, 1 H), 8.75 (d,  $J$  = 8.4 Hz, 1 H), 8.23-8.14 (m, 2 H), 7.87-7.73 (m, 2 H), 7.44 (dd,  $J$  = 10.2, 8.3 Hz, 1 H), 7.34-7.29 (m, 5 H), 7.03 (t,  $J$  = 8.2 Hz, 1 H), 6.66-6.56 (m, 3 H), 4.93 (s, 2 H); MS (ESI+) for  $\text{C}_{23}\text{H}_{18}\text{FN}_3\text{O}_3\text{S}$   $m/z$  407 (M+H) $^+$ .

30       The final product was prepared according to Method F: Yield 0.6g (78%);  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  10.67 (s, 1 H), 9.30 (br. s, 2 H), 8.69 (d,  $J$  = 7.7 Hz, 1 H), 8.21 (d,  $J$  = 8.4 Hz, 1

H), 8.13 (d,  $J = 8.2$  Hz, 1 H), 7.75-7.61 (m, 2 H), 7.35-7.30 (m, 5 H), 7.19 (d,  $J = 8.2$  Hz, 1 H), 7.03 (t,  $J = 8.2$  Hz, 1 H), 6.68-6.54 (m, 3 H), 4.93 (s, 2 H), 3.36-3.29 (m, 8 H); MS (ESI+) for C<sub>27</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>S  $m/z$  474 (M+H)<sup>+</sup>.

#### 5 EXAMPLE 112

*N*-(4-fluorophenyl)-4-piperazin-1-yl naphthalene-1-sulfonamide, hydrochloride  
*N*-(4-fluorophenyl)naphthalene-1-sulfonamide- Method E: Use of 4-methoxyaniline afforded the title compound (475 mg, 86%) as an oil by the application of the general procedure A described above. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.79-8.71 (m, 1H), 8.23-8.10 (m, 2H), 7.75-7.59 (2H),  
 10 7.52-7.45 (m, 1H), 7.15-7.04 (m, 1H), 6.96-6.73 (m, 4H); MS  $m/z$  (M+1) 320.

The final product was prepared according to Method F: Use of 4-fluoro-*N*-(4-fluorophenyl)naphthalene-1-sulfonamide afforded the title compound (95 mg, 15%), after recrystallization from methanol, as a white solid by the application of the general procedure B described above. <sup>1</sup>H NMR (DMSO) δ 10.60 (s, 1H), 9.37 (br s, 2H), 8.73-8.65 (m, 1H),  
 15 8.25-8.17 (m, 1H), 8.13-8.06 (m, 1H), 7.76-7.60 (m, 2H), 7.22-7.15 (m, 1H), 7.04-6.95 (m, 4H), 3.43-3.24 (m, 8H); MS  $m/z$  (M+1) 386.

#### EXAMPLE 113

*N*-(3-Ethylphenyl)-4-piperazin-1-yl naphthalene-1-sulfonamide, hydrochloride

20 *N*-(3-Ethylphenyl)-4-fluoronaphthalene-1-sulfonamide -Method E: yield 80%, purity 92%. <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) δ ppm 1.03 (t,  $J = 7.52$  Hz, 3 H), 2.45 (q,  $J = 7.65$  Hz, 2 H), 6.68-6.72 (m, 2 H, N-H), 6.87 (d,  $J = 7.13$  Hz, 1 H), 6.99-7.13 (m, 2H), 7.65-7.72 (m, 2 H), 8.13-8.20 (m, 2 H), 8.65 (d,  $J = 8.44$  Hz, 1 H); MS (ESI+) for C<sub>18</sub>H<sub>16</sub>F N O<sub>2</sub> S  $m/z$  329.393 (M+H)<sup>+</sup>. 330.0; MS (ESI-) for C<sub>18</sub>H<sub>16</sub>F N O<sub>2</sub> S  $m/z$  329.393 (M-H)<sup>-</sup>. 328.1

25 The final product was prepared according to Method F: yield 61%, purity 98%. <sup>1</sup>H NMR (500 MHz, DMSO) δ 8.67-8.65 (m, 1H), 8.16-8.10 (m, 2H), 7.66-7.57 (m, 2H), 7.14 (d,  $J = 8.56$  Hz, 1H), 6.97-6.94 (m, 1H), 6.78-6.76 (m, 2H), 6.70-6.69 (m, 1H), 3.30-3.28 (m, 2H), 3.22-3.19 (m, 2H), 2.34 (q,  $J = 17$  Hz, 2H), 1.94 (tr,  $J = 17$  Hz, 3H); MS (ESI+) for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>S HCl  $m/z$  431.98 (M-HCl+H)<sup>+</sup>. 396.1; MS (ESI-) for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>S  
 30 HCl  $m/z$  (M-HCl-H)<sup>-</sup>. 394.1

## EXAMPLE 114

**4-Piperazinyl-N-[3-(trifluoromethyl)phenyl]naphthalene-1-sulfonamide, hydrochloride**

The final product was prepared according to Method F: Use of 4-fluoro-N-(3-trifluoromethylthiophenyl)naphthalene-1-sulfonamide afforded the title compound (0.08 g),  
5 gave 0.060 g of the desired product, yield 85%, purity 96%.

<sup>1</sup>H NMR (270 MHz, CD<sub>3</sub>OD) δ 8.74-8.71 (m, 1H), 8.26-8.19 (m, 2H), 7.75-7.65 (m, 2H), 7.32 (br.s, 1H), 7.23-7.14 (m, 4H), 3.57-3.47 (m, 4H), 3.35-3.30 (m, 4H); MS (ESI+) for C<sub>21</sub> H<sub>20</sub> F<sub>3</sub> N<sub>3</sub> O<sub>2</sub> S<sub>2</sub> HCl *m/z* 467.09 +35.46 (M+H)<sup>+</sup> 468.0; MS (ESI+) for C<sub>21</sub> H<sub>20</sub> F<sub>3</sub> N<sub>3</sub> O<sub>2</sub> S<sub>2</sub> HCl *m/z* 467.09 +35.46 (M-H)<sup>-</sup> 466.1.

10

## EXAMPLE 115

**4-Piperazinyl-N-[3-benzoylphenyl]naphthalene-1-sulfonamide, hydrochloride**

The final product was prepared according to Method F: yield 25%, purity 97%.

<sup>1</sup>H NMR (270 MHz, CD<sub>3</sub>OD) δ 8.76-8.72 (m, 1H), 8.29-8.26 (m, 1H), 8.17 (d, J= 8,1 Hz, 1H), 7.73-7.60 (m, 3H), 7.55-7.44 (m, 4H), 7.34-7.28 (m, 4H), 7.18 (d, J= 8,1 Hz, 1H), 3.54-  
15 3.50 (m, 4H), 3.37-3.30 (m, 4H); MS (ESI+) for C<sub>27</sub> H<sub>25</sub> N<sub>3</sub> O<sub>3</sub> S HCl *m/z* 471.17 +35.46 (M+H)<sup>+</sup> 472.1; MS (ESI+) for C<sub>27</sub> H<sub>25</sub> N<sub>3</sub> O<sub>3</sub> S HCl *m/z* 471.17 +35.46 (M-H)<sup>-</sup> 470.01.

## EXAMPLE 116

20 **4-Piperazinyl-N-[3-(4-bromo-1-methyl-1H-pyrazol-3-yl)phenyl]naphthalene-1-sulfonamide, hydrochloride**

The final product was prepared according to Method F: yield 81%, purity 96%.

<sup>1</sup>H NMR (270 MHz, CD<sub>3</sub>OD) δ 8.78-8.74 (m, 1H), 8.27-8.24 (m, 1H), 8.19 (d, J= 8,1 Hz, 1H), 7.75-7.64 (m, 2H), 7.46 (s, 1H), 7.31-7.25 (m, 1H), 7.19-7.16 (m, 2H), 7.02-6.96 (m,  
25 2H), 3.57-3.49 (m, 4H), 3.52 (s, 3H), 3.35-3.30 (m, 4H); MS (ESI+) for C<sub>24</sub> H<sub>24</sub> Br N<sub>5</sub> O<sub>2</sub> S HCl *m/z* 525.08 + 35.46 (M+H)<sup>+</sup> 526.0; MS (ESI+) C<sub>24</sub> H<sub>24</sub> Br N<sub>5</sub> O<sub>2</sub> S HCl *m/z* 525.08 + 35.46 (M-H)<sup>-</sup> 524.1.

## EXAMPLE 117

30 **4-Piperazinyl-N-[3-biphenylphenyl]naphthalene-1-sulfonamide, hydrochloride**

The final product was prepared according to Method F: yield 33%, purity 95%.

<sup>1</sup>H NMR (270 MHz, CD<sub>3</sub>OD) δ 8.83-8.80 (m, 1H), 8.26-8.22 (m, 2H), 7.79-7.68 (m, 2H), 7.39-7.35 (m, 5H), 7.23-7.19 (m, 4H), 7.03-6.99 (m, 1H), 3.52-3.47 (m, 4H), 3.35-3.30 (m, 4H); MS (ESI+) for C<sub>26</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>S HCl *m/z* 443.17 + 36.45 (M+H)<sup>+</sup> 444.1; MS (ESI-) for C<sub>26</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>S HCl *m/z* 443.17 + 36.45 (M-H)<sup>-</sup> 442.2.

5

## SYNTHESIS OF EXAMPLES AND INTERMEDIATES IN TABLE IV

## General Method H

## 10 EXAMPLE 118

**N-[1-(4-Methyl-1-piperazinyl)-3-isoquinolinyl]benzenesulfonamide, hydrochloride**

To a solution of 1-(4-methyl-1-piperazinyl)-3-isoquinolinylamine (commercially available; 0.26 g, 1.07 mmol) and pyridine (0.60 mL, 7.51 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added benzenesulfonyl chloride (151 μL, 1.18 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL). The mixture was stirred at room temperature for 16 hours and left in the refrigerator for 24 hours. The precipitate was collected by filtration to give 0.255 g (57%) of the pure product as the HCl-salt: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.93 (s, 2H), 7.96-7.90 (m, 3H), 7.79-7.75 (m, 1H), 7.64-7.56 (m, 4H), 7.44-7.38 (m, 1H), 7.01 (s, 1H), 3.70-3.15 (m, partly obscured by solvent signal, 8H), 2.79 (s, 3H); MS (posEI-DIP) *m/z* 382 (M<sup>+</sup>).

20

## EXAMPLE 119

**2,4-di-Fluoro-N-[1-(4-methyl-1-piperazinyl)-3-isoquinolinyl]benzenesulfonamide, hydrochloride**

The title compound was prepared from 1-(4-methyl-1-piperazinyl)-3-isoquinolinylamine (commercially available; 0.209 g, 0.862 mmol) using the method described in the example that follows: yield 0.152 g (65%); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 11.35 (s, 1H), 11.09 (br s, 1H), 8.15-8.04 (m, 1H), 7.97-7.90 (m, 1H), 7.83-7.35 (m, 5H), 6.95 (s, 1H), 3.70-3.10 (m, 8H), 2.85-2.75 (m, 3H); MS (posESI) *m/z* 419 (M+H).

## EXAMPLE 120

**4-Bromo-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride**

5  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 11.07 (s, 1H), 10.75 (br s, 1H), 7.98-7.75 (m, 5H), 7.66-7.58 (m, 1H), 7.52 (s, 1H), 7.47-7.37 (m, 1H), 7.00 (brs, 1H), 3.70-3.20 (obscured in part by solvent signal, 8H), 2.85-2.80 (m, 2H), MS (posESI)  $m/z$  = 461 (M+H)

## EXAMPLE 121

10 **5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-amide, hydrochloride**

$^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 11.47 (br s, 1H), 10.55 (br s, 1H), 8.14-8.07 (m, 1H), 8.01-7.98 (m, 1H), 7.96-7.98 (m, 1H), 7.82-7.76 (m, 1H), 7.67-7.52 (m, 2H), 7.47-7.39 (m, 1H), 7.06 (s, 1H), 3.80-3.65 (m, 2H), 3.60-3.25 (m, obscured by solvent signal), 2.80-2.73 (m, 15 3H), ), MS (posESI)  $m/z$  = 487 (M+H)

## EXAMPLE 122

**3-Chloro-2-methyl-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride**

20  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 11.24 (br s, 1H), 10.56 (br s, 1H), 8.10-8.05 (m, 1H), 7.95-7.89 (m, 1H), 7.80-7.69 (m, 2H), 7.66-7.57 (m, 1H), 7.53-7.35 (m, 2H), 6.94 (s, 1H), 3.70-3.30 (m, obscured by solvent signal), 3.29-3.10 (m, 4H), 3.85-2.79 (m, 3H), ), MS (posESI)  $m/z$  = 431(M+H).

## 25 EXAMPLE 123

**3,4-Dichloro-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride**

$^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 11.17 (s, 1H), 10.50 (br s, 1H), 8.16-8.14 (m, 1H), 7.98-7.93 (m, 1H), 7.91-7.89 (m, 2H), 7.85-7.80 (m, 1H), 7.68-7.60 (m, 1H), 7.49-7.41 (m, 1H), 7.04 (s, 1H), 3.85-3.20 (m, obscured by solvent signal), 2.87-2.83 (m, 3H), ), MS (posESI)  $m/z$  = 30 451(M+H).

## EXAMPLE 124

**4-Methyl-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride**

5  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 10.88 (m, brs, 1H), 7.95-7.88 (m, 1H), 7.85-7.74 (m, 3H), 7.65-7.56 (m, 1H), 7.51-7.34 (m, 4H), 7.14-7.09 (m, 1H), 6.99 (s, 1H), 3.75-3.45 (m, obscured by solvent signal, 4H), 3.35-3.15 (m, 4H), 2.84 (d,  $J = 4.75$  Hz, 3H), 2.33 (s, 3H), ), MS (posESI)  $m/z = 397(\text{M}+\text{H})$ .

## 10 EXAMPLE 125

**3-Methoxy-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride**

$^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 10.93 (brs, 1H), 10.69 (brs, 1H), 7.93 (d,  $J = 8.19$  Hz, 1H), 7.79 (d,  $J = 7.92$  Hz, 1H), 7.65-7.57 (m, 1H), 7.52-7.37 (m, 4H), 7.24-7.13 (m, 1H), 7.03 (s, 15 1H), 3.78 (s, 3H), 3.75-3.20 (m, obscured by solvent signal, 8H), 2.81 (d,  $J = 4.48$  Hz, 3H), MS (posESI)  $m/z = 413(\text{M}+\text{H})$ .

## EXAMPLE 126

**5-Chloro-thiophene-2-sulfonic acid [1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-amide, hydrochloride**

$^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 7.76-7.21 (m, 1H), 7.01-6.96 (m, 1H), 6.89-6.82 (m, 1H), 6.74-6.71 (m, 1H), 6.70-6.66 (m, 1H), 6.40 (brs, 1H), 6.22 (d,  $J = 3.96$  Hz, 1H), 3.20-3.10 (m, 2H), 2.87-2.75 (m, 2H), 2.70-2.50 (m, obscured in part by solvent signal, 4H), 2.19 (brs, 3H), MS (posESI)  $m/z = 423(\text{M}+\text{H})$ .

25

## EXAMPLE 127

**N-{2-Chloro-4-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-ylsulfamoyl]-phenyl}-acetamide, hydrochloride**

$^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 10.03 (s, 1H), 10.52 (brs, 1H), 7.93 (d,  $J = 8.44$  Hz, 1H), 7.78 (d,  $J = 7.92$  Hz, 1H), 7.71 (d,  $J = 2.11$  Hz, 1H), 7.65-7.57 (m, 1H), 7.57-7.51 (dd,  $J = 2.11$  and 8.44 Hz, 1H), 7.45-7.37 (m, 1H), 6.99 (s, 1H), 6.80 (d, 8.44 Hz, 1H), m3.82-3.71 30

(m, 2H), 3.60-3.20 (m, obscured by solvent signal) 2.84 (d,  $J = 4.49$  Hz, 3H), MS (posESI)  $m/z = 474(M+H)$ .

#### EXAMPLE 128

5    **2,5-Dichloro-thiophene-3-sulfonic acid [1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-amide, hydrochloride**

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 7.94-7.89 (m, 1H), 7.77-7.72 (m, 1H), 7.63-7.56 (m, 1H), 7.46 (s, 1H), 7.44-7.36 (m, 1H), 3.50-3.20 (m, obscured by solvent signal), 2.70-2.50 m, obscured by solvent signal), 2.32 (brs, 3H), MS (posESI)  $m/z = 457(M+H)$ .

10

#### EXAMPLE 129

**N-[1-(4-Methyl-piperazin-1-yl)-isoquinolin-3-yl]-3-trifluoromethyl-benzenesulfonamide, hydrochloride**

15     $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 11.17 (s, 1H), 10.71 (brs, 1H), 8.27-8.17 (m, 2H), 8.07-8.01 (m, 1H), 7.97-7.79 (m, 3H), 7.67-7.60 (m, 1H), 7.48-7.40 (m, 1H), 7.06 (s, 1H), 3.70-3.40 (m, m, obscured by solvent signal), 3.31-3.14 (m, 4H), 2.82 (d,  $J = 4.75$  Hz, 3H), MS (posESI)  $m/z = 451(M+H)$ .

#### EXAMPLE 130

20    **N-[1-(4-Methyl-piperazin-1-yl)-isoquinolin-3-yl]-4-phenoxy-benzenesulfonamide, hydrochloride**

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 10.91 (s, 1H), 10.79 (brs, 1H), 7.98-7.89 (m, 3H), 7.81-7.74 (m, 1H), 7.66-7.55 (m, 1H), 7.49-7.37 (m, 3H), 7.28-7.20 (m, 1H), 7.13-7.06 (m, 4H), 7.00 (s, 1H), 3.77-3.66 (m, 2H), 3.50-3.20 (m, 6H), 2.82 (d,  $J = 4.49$  Hz, 3H), MS (posESI)  $m/z =$   
25    475 (M+H).

#### EXAMPLE 131

**5-Bromo-2-methoxy-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride**

30     $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 10.90 (s, 1H), 10.75 (brs, 1H), 7.99 (d,  $J = 2.64$  Hz, 1H), 7.91 (m, d,  $J = 8.45$  Hz, 1H), 7.80-7.73 (m, 2H), 7.65-7.57 (m, 1H), 7.45-7.37 (m, 1H), 7.14

(d,  $J = 8.47$  Hz, 1H), 3.82 (s, 3H), 3.68-3.55 (m, 2H), 3.52-3.38 (m, 2H), 3.35-3.20 (m, 4H), 2.84 (d,  $J = 4.49$  Hz, 3H), MS (posESI)  $m/z = 491$ (M+H).

**EXAMPLE 132**

5 **2-Methanesulfonyl-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride**

MS (posESI)  $m/z = 461$  (M+H).

**EXAMPLE 133**

10 **3,5-Dimethyl-isoxazole-4-sulfonic acid [1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-amide, hydrochloride**

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 11.17 (s, 1H), 10.54 (s, 1H), 7.99 (d,  $J = 8.45$  Hz, 1H), 7.86 (d,  $J = 7.92$  Hz, 1H), 7.71-7.63 (m, 1H), 7.53-7.45 (m, 1H), 7.07 (s, 3H), 3.75-3.64 (m, 2H), 3.55-3.45 (m, 2H), 3.35-3.15 (m, 4H), 2.84 (d,  $J = 4.49$  Hz, 3H), 2.76 (s, 3H), 2.31 (s, 3H),

15 MS (posESI)  $m/z = 402$  (M+H).

**EXAMPLE 134**

**2,4,6-Trimethyl-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide**

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 10.82 (s, 1H), 10.52 (brs, 1H), 7.92-7.87 (m, 1H), 7.76-7.70 (m, 1H), 7.64-7.56 (m, 1H), 7.43-7.36 (m, 1H), 7.00 (s, 2H), 6.88 (s, 1H), 6.74 (brs, 1H), 3.60-3.10 (m, 8H), 2.81 (d,  $J = 4.75$  Hz, 3H), 2.61 (s, 6H), 2.22 (s, 3H), MS (posESI)  $m/z = 425$  (M+H)..

**EXAMPLE 135**

25 **3,4-Dimethoxy-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide, hydrochloride**

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 10.75 (brs, 1H), 10.72 (s, 1H), 7.95-7.90 (m, 1H), 7.82-7.76 (m, 1H), 7.65-7.57 (m, 1H), 7.55-7.37 (m, 2H), 7.11 (d,  $J = 8.71$  Hz, 1H), 7.05 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.76-3.69 (m, obscured in part by -OMe), 3.51-3.19 (m, 6H), 2.82 (d,  $J = 4.49$  Hz, 3H), MS (posESI)  $m/z = 443$  (M+H).



## SYNTHESIS OF EXAMPLES IN TABLE V

## EXAMPLE 136

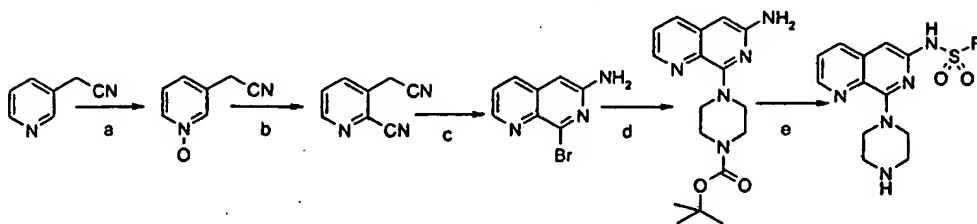
**N-[8-(4-Methyl-1-piperazinyl)-5-quinolinyl]benzenesulfonamide, hydrochloride**

- 5 To a solution of 8-(4-methyl-1-piperazinyl)-5-nitroquinoline (0.379 g, 1.39 mmol) in THF:EtOH 1:4 solvent system was added Raney-Ni (1.0 mL suspension in EtOH) followed by hydrazine hydrate (0.348 g, 6.95 mmol). The mixture was stirred vigorously at room temperature for 16 hours and then filtered through celite pretreated with water. The filtrate was concentrated, and the residue was purified by column chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 9:1:0.4%) to give 0.337 g of 8-(4-methyl-1-piperazinyl)-5-
- 10 quinolinylamine. The amine was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (6.0 mL) and pyridine (0.785 mL, 9.73 mmol) and benzenesulfonyl chloride (0.178 mL, 1.39 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours and then washed with saturated aqueous NaHCO<sub>3</sub>. The organic phase was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The
- 15 crude product was purified by column chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 9:1:0.4%) to give 0.130 g of the free base which was converted to its HCl-salt: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ; 11.09 (br s, 1H), 10.32 (s, 1H), 8.94-8.89 (m, 1H), 8.55-8.48 (m, 1H), 7.68-7.65 (m, 2H), 7.64-7.57 (m, 2H), 7.54-7.49 (m, 2H), 7.27-7.22 (m, 1H), 7.12-7.08 (m, 1H), 3.95-3.84 (m, 2H), 3.55-3.49 (m, 2H), 3.45-3.35 (m, 2H), 3.26-3.16 (m, 2H), 2.85-2.82 (m, 3); MS
- 20 (posESI) *m/z* 383 (M+H).

## SYNTEHSIS OF EXAMPLES AND INTERMEDIATES IN TABLE VI

## Scheme 3

25



a) H<sub>2</sub>O<sub>2</sub>, CH<sub>3</sub>COOH, 100 °C; b) Me<sub>3</sub>SiCN, Toluene, (Me)<sub>2</sub>N-CO-Cl, 65 °C; c) HBr/  
CH<sub>3</sub>COOH, rt; d) Boc-Piperazine, K<sub>2</sub>CO<sub>3</sub>, 90 °C; R-SO<sub>2</sub>Cl, py, rt.

#### 5 **INTERMEDIATE 20**

3-Cyanomethylpyridine-*N*-oxide - Hydrogenperoxide (17 ml, 30 % ww) was added to  
a mixture of 3-cyanomethylpyridine (11 g, 93 mmol) and glacial acetic acid (55 ml) and  
heated at 100°C overnight. The mixture was diluted with water (70ml) and MnO<sub>2</sub> (5.0 g) was  
carefully added and stirred for 5 hours (check peroxide content with peroxide sticks), and  
10 only small amounts of peroxide was left. The mixture was concentrated in vacuo to 40 ml  
and diluted with methanol (40 ml), filtered through a short plug of silica, and washed with  
methanol (400 ml). The filtrate were concentrated and recrystallized from chloroform and  
hexane to give the title compound (9.5 g, 76%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.16 (s, 2H), 7.32 (s,  
2H), 3.73 (s, 2H); MS m/z (M+1)135.

15

#### **INTERMEDIATE 21**

3-(Cyanomethyl)pyridine-2-carbonitrile - Trimethylsilylcyanide (4.2 ml, 32 mmol)  
was added to a suspension of 3-cyanomethylpyridine-*N*-oxide (3.5 g, 26 mmol) in toluene  
(35 ml) and after 1 minute dimethylcarbamyldichloride (2.4 ml, 26 mmol) was added and the  
20 reaction was stirred overnight at 65°C. EtOAc and 1N NaOH was added and the mixture was  
washed with water (2x). The organic phase was dried (MgSO<sub>4</sub>) and evaporated. The crude  
product was dissolved in ethanol (150 ml) and stirred overnight, filtered (remove byproduct)  
and concentrated (25 ml). After 30 min at 0°C the yellow powder was filtered and washed  
with cold ethanol (1x) to give, after drying, the title compound (2.15 g, 57%). <sup>1</sup>H NMR  
25 (CDCl<sub>3</sub>) δ 8.71 (m, 1 H), 8.03 (d, J = 8.03 Hz, 1H), 7.62 (dd, J = 8.16, 4.64 Hz, 1H), 4.04 (s,  
2H); MS m/z (M-1) 142.

#### **INTERMEDIATE 22**

6-Amino-8-bromo-1,7-naphthyridine - 3-(Cyanomethyl)pyridine-2-carbonitrile (4.0 g,  
30 28 mmol) was added carefully to HBr in acetic acid (33%) (25 ml) at rt. The red suspension  
was stirred for 1.5 h and filtered. The red solid was washed with EtOAc (3x) and suspended

in water. 1N NaOH was added dropwise until pH-8, and the suspension was stirred for 45 minutes and filtered. The red solid was washed with water (2x) and dried. The crude product was suspended in 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> and filtered through a short plug of silica, washing with 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>. Subsequent concentration in vacuo afforded the title compound  
5 (3.85 g, 61%). <sup>1</sup>H NMR (DMSO) δ 8.58 (dd, J = 4.02, 1.51 Hz, 1H), 8.01 (dd, J = 8.53, 1.51 Hz, 1H), 7.47 (dd, J = 8.53, 4.02 Hz, 1H), 6.58 (s, 1H), 6.48 (s, 2H); MS m/z (M+1) 226.

### INTERMEDIATE 23

*tert*-Butyl 4-(6-amino-1,7-naphthyridin-8-yl)piperazine-1-carboxylate - A mixture of  
10 6-amino-8-bromo-1,7-naphthyridine (650 mg, 2.9 mmol), BOC-piperazine (1.1 g, 5.9 mmol), potassium carbonate (2 g, 15 mmol) in DMSO (1 ml) was stirred at 90°C for 3 days. Chloroform was added, the mixture was filtered and the filtrate was washed with brine (3 x 100 ml). The organic phase was dried using potassium carbonate, filtered and concentrated in vacuo to give a yellow oil. The oil was triturated with diethyl ether and then eluted through a  
15 short silica plug using chloroform. Subsequent concentration of the residue in vacuo gave the title compound (700 mg, 74%) as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.43 (dd, J = 4.09, 1.72 Hz, 1H), 7.67 (dd, J = 8.31, 1.72 Hz, 1H), 7.25-7.20 (m, 1H), 6.08 (s, 1H), 4.29 (s, 2 H), 3.95-3.88 (m, 4H), 3.65-3.57 (m, 4H), 1.46 (s, 9 H); MS m/z (M+1) 330.

### 20 General Procedure I

To a stirred solution of *tert*-butyl 4-(6-amino-1,7-naphthyridin-8-yl)piperazine-1-carboxylate (63 mg, 0.19 mmol) in anhydrous dichloromethane (0.5 ml) and pyridine (0.25 ml) was added *p*-toluenesulfonyl chloride (36 mg, 0.19 mmol). The reaction mixture was  
25 stirred at room temperature over night and then concentrated *in vacuo*. The residue was purified using reversed-phase preparative HPLC to give the corresponding *tert*-butoxycarbonyl protected piperazine intermediate. This was dissolved in dichloromethane (1.5 ml) and treated with concentrated TFA (1 ml) at room temperature for 1.5 hours.

## EXAMPLE 137

**4-Methyl-*N*-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic acid**

The title compound was prepared following the general procedure I (61 mg, 65%) as a yellow solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.57-8.65 (m, 1H), 8.06-7.98 (m, 1H), 7.86-7.78 (m, 2H), 7.53-7.43 (m, 1H), 7.36-7.26 (m, 2H), 6.88 (s, 1H), 4.18-4.06 (m, 4H), 3.35-3.24 (m, 4H), 2.35 (s, 3H); MS *m/z* (M+1) 384.

## EXAMPLE 138

**4-Bromo-*N*-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic acid**

The title compound was prepared following the general procedure I (14 mg, 13%). <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.70-8.63 (m, 1H), 8.14-8.05 (m, 1H), 7.91-7.83 (m, 2H), 7.76-7.67 (m, 2H), 7.57-7.49 (m, 1H), 6.91 (s, 1H), 4.19-4.09 (m, 4H), 3.38-3.28 (m, 4H); MS *m/z* (M+1) 449.

## EXAMPLE 139

***N*-(8-Piperazin-1-yl-1,7-naphthyridin-6-yl)naphthalene-1-sulfonamide, trifluoroacetic acid**

The title compound was prepared following the general procedure I (66 mg, 65%). <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.82-8.76 (m, 1H), 8.58-8.54 (m, 1H), 8.42-8.37 (m, 1H), 8.13-8.07 (m, 1H), 8.01-7.92 (m, 2H), 7.71-7.54 (m, 3H), 7.47-7.40 (m, 1H), 6.80 (s, 1H), 4.02-3.96 (m, 4H), 3.24-3.18 (m, 4H); MS *m/z* (M+1) 420.

## EXAMPLE 140

***N*-(8-Piperazin-1-yl-1,7-naphthyridin-6-yl)butane-1-sulfonamide, trifluoroacetic acid**

The title compound was prepared following the general procedure I (48 mg, 55%). <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.71-8.66 (m, 1H), 8.13-8.06 (m, 1H), 7.58-7.51 (m, 1H), 6.83 (s, 1H), 4.33-4.23 (m, 4H), 3.51-3.38 (m, 6H), 1.91-1.72 (m, 2H), 1.53-1.38 (m, 2H), 0.98-0.86 (m, 3H); MS *m/z* (M+2) 351.

## EXAMPLE 141

**3-Trifluoromethyl-*N*-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic acid**

The title compound was prepared following the general procedure I (60 mg, 57%).

5  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.70-8.63 (m, 1H), 8.28-8.17 (m, 2H), 8.13-8.05 (m, 1H), 7.96-7.87 (m, 1H), 7.80-7.69 (m, 1H), 7.58-7.48 (m, 1H), 6.93 (s, 1H), 4.18-4.07 (m, 4H), 3.39-3.27 (m, 4H); MS  $m/z$  (M+1) 438.

## EXAMPLE 142

10 **3,4-Dimethoxy-*N*-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic acid**

The title compound was prepared following the general procedure I (65 mg, 63%).

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.68-8.59 (m, 1H), 8.11-8.01 (m, 1H), 7.61-7.40 (m, 3H), 7.04-6.92 (m, 2H), 4.22-4.10 (m, 4H), 3.81 (s, 3H), 3.78 (s, 3H), 3.39-3.27 (m, 4H); MS  $m/z$  (M+1)  
15 430.

## EXAMPLE 143

**2,4-Dichloro-*N*-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic acid**

20 The title compound was prepared following the general procedure I (56 mg, 53%).

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.66-8.61 (m, 1H), 8.25-8.20 (m, 1H), 8.06-8.00 (m, 1H), 7.65-7.61 (m, 1H), 7.57-7.47 (m, 2H), 6.76 (s, 1H), 4.13-4.06 (m, 4H), 3.36-3.28 (m, 4H); MS  $m/z$  (M+2) 439.

## 25 EXAMPLE 144

***N*-(8-Piperazin-1-yl-1,7-naphthyridin-6-yl)thiophene-2-sulfonamide, trifluoroacetic acid**

The title compound was prepared following the general procedure I (57 mg, 61%).

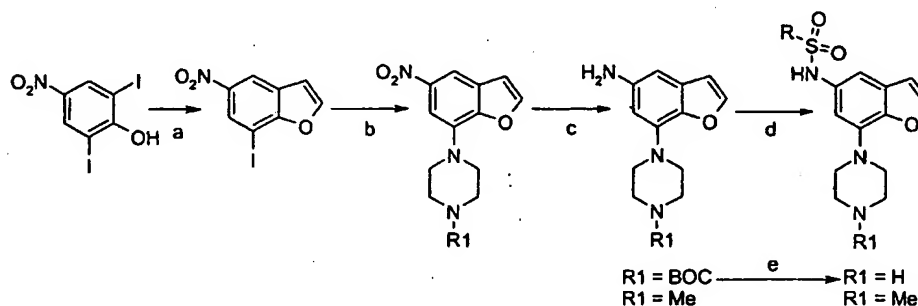
$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.71-8.64 (m, 1H), 8.14-8.05 (m, 1H), 7.76-7.67 (m, 2H), 7.58-7.49 (m, 1H), 7.11-7.03 (m, 1H), 6.98 (s, 1H), 4.27-4.15 (m, 4H), 3.40-3.28 (m, 4H); MS  $m/z$   
30 (M+1) 376.

## EXAMPLE 145

**1-Phenyl-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)methanesulfonamide, trifluoroacetic acid**

The title compound was prepared following the general procedure I (35 mg, 37%). <sup>1</sup>H NMR (DMSO)  $\delta$  8.83 (br s, 1H), 8.52-8.40 (m, 2H), 7.47-7.41 (m, 1H), 7.29-7.10 (m, 6H), 6.87 (s, 1H), 4.52 (s, 2H), 4.39-4.31 (m, 4H), 3.30-3.22 (m, 4H); MS  $m/z$  (M+1) 384.

## SYNTHESIS OF EXAMPLES AND INTERMEDIATES IN TABLE

10 **Scheme 4**

Scheme 4 a) TMS-acetylene, Cu<sub>2</sub>O, Py, 80 °C; b) tBuO-Na, Pd<sub>2</sub>(dba)<sub>3</sub>, Xantphos, xylene, 120 °C; c) Raney-Ni, Hydrazine, THF/Ethanol; d) R-SO<sub>2</sub>-Cl, Py; e) HCl-diethyl ether.

15

**INTERMEDIATE 24**

**7-Iodo-5-nitro-1-benzofuran** - A mixture of 4-nitro-2,5-diiodophenol (7.68 g, 6.86 mmol), TMS-acetylene (0.67g, 6.86 mmol) and Cu<sub>2</sub>O (0.59 g, 4.12 mmol) in pyridine (120 mL) was heated to 80 C for 48 h. The mixture was filtered through celite and the solvent was removed. Column chromatography DCM/heptane 1:1 gave 0.35 g (18 %) of product.

<sup>1</sup>HNMR (CD<sub>3</sub>OD)  $\delta$  8.60 (d, 1H,  $J = 2.1$  Hz), 8.51 (d, 1H,  $J = 2.1$  Hz), 7.84 (d, 1H,  $J = 2.1$  Hz), 7.04 (d, 1H,  $J = 2.4$  Hz); MS (ESI) 289.8 (M + H)<sup>+</sup>; Purity (HPLC, column X) 93%.

**INTERMEDIATE 25**

**1-Methyl-4-(5-Nitro-1-benzofuran-7-yl)-piperazine** - A mixture of 7-iodo-5-nitro-1-benzofuran (94.5 mg, 0.327 mmol), Xantphos (19 mg, 0.032 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (7.4 mg, 0.025 mmol) and NaOt-Bu (44.0 mg, 0.458 mmol), methylpiperazine (39.3 mg, 0.392 mmol)

in xylene (3 mL) was heated to 120 °C overnight. The mixture was diluted with DCM and filtered through silica. The product was elueed with DCM/MeOH x 0.4 % NH<sub>3</sub>. Flash chromatography (DCM/MeOH x 0.4 % NH<sub>3</sub>) gave 60 mg (70 %) of BVT: <sup>1</sup>HNMR (CD<sub>3</sub>OD) δ 8.07 (d, 1H, J = 2.1 Hz), 7.70 (d, 1H, J = 2.1 Hz), 7.58 (d, 1H, J = 2.1 Hz), 6.84 (d, 1H, J = 2.1 Hz), 3.44-3.40 (m, 4H), 2.65-2.62 (m, 4H), 2.36 (s, 3H); MS (ESI) 262.0 (M + H)<sup>+</sup>; Purity (HPLC, column X) 95%.

#### INTERMEDIATE 26

*tert-Butyl 4-(5-nitro-1-benzofuran-7-yl)-piperazine-1-carboxylate*- The title compound was prepared according to the same procedure used for Intermediate 25 using N-tert-butyl-piperazine carboxylate to afford 240 mg (64 %) of a white solid: <sup>1</sup>HNMR (CD<sub>3</sub>OD) δ 8.08 (d, 1H, J = 2.1 Hz), 7.72 (d, 1H, J = 2.1 Hz), 7.58 (d, 1H, J = 2.1 Hz), 6.86 (d, 1H, J = 2.1 Hz), 3.66-3.62 (m, 4H), 3.34-3.31 (m, 4H), 1.46 (s, 9H); MS (ESI) 370.0 (M + Na)<sup>+</sup>; Purity (HPLC, column X) 96%.

#### INTERMEDIATE 27

*1-Methyl-4-(5-amino-1-benzofuran-7-yl)-piperazine*

#### INTERMEDIATE 28

*tert-Butyl 4-(5-amino-1-benzofuran-7-yl)-piperazine-1-carboxylate* -1-Methyl-4-(5-Nitro-1-benzofuran-7-yl)-piperazine (1 eq) and *tert-butyl 4-(5-nitro-1-benzofuran-7-yl)-piperazine-1-carboxylate* (1 eq) were reduced to aromatic amine with Raney-Ni and hydrazine (10 eq) in THF/Ethanol (1:4), 3h at room temperature. The reaction mixture are filtered through celite pad, the volatiles are evaporated and the crude is used in the next reactions.

#### EXAMPLE 146

**3-Cyanophenyl-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride**

To a solution of *tert-butyl 4-(5-amino-1-benzofuran-7-yl)-piperazine-1-carboxylate* (43 mg 0.138 mmol) and pyridine (100 μL, 1.24 mmol) was added 3-

cyanobenzenesulfonylchloride (33.4 mg, 0.166 mmol). After 2 h PS-Trisamin was added and the reaction was stirred overnight. Flash chromatography (DCM/Heptane/MeOH 5:4:1) gave 24.6 mg of a solid. The crude product was dissolved in MeOH (2mL) and HCl/ether 2M (4 mL) was added. After 0.5 h the sample was concentrated to afford 19 mg (36 %) of a white solid: <sup>1</sup>HNMR (CD<sub>3</sub>OD) δ 8.02-7.88 (m, 3H), 7.72 (d, 1H, J = 2.1 Hz), 7.76-7.61 (m, 1H), 6.92 (d, 1H, J = 2.1 Hz), 6.74 (d, 1H, J = 2.1 Hz), 6.60 (d, 1H, J = 2.1 Hz), 3.52-3.41 (m, 8H); MS (ESI) 381.2 (M + H)<sup>+</sup>; Purity (HPLC, column X) 95%.

#### EXAMPLE 147

**4-Phenoxy-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride**  
The title compound was prepared according to the method used for the synthesis of Example 146 (21 %) of a white solid: <sup>1</sup>HNMR (CD<sub>3</sub>OD) δ 7.73 (d, 1H, J = 2.1 Hz), 7.69-7.64 (m, 2H), 7.43-7.37 (m, 2H), 7.24-7.17 (m, 1H), 7.04-6.94 (m, 4H), 6.88 (d, 1H, J = 2.1 Hz), 6.74 (d, 1H, J = 2.1 Hz), 6.70 (d, 1H, J = 2.1 Hz), 3.53-3.41 (m, 8H); MS (ESI) 450.1 (M + H)<sup>+</sup>; Purity (HPLC, column X) 90 %.

#### EXAMPLE 148

**1-Naphthyl-Phenoxy-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride**

The title compound was prepared according to the method used for the synthesis of Example 146 (30 %) of a white solid: <sup>1</sup>HNMR (CD<sub>3</sub>OD) δ 8.65 (d, 1H, J = 8.8 Hz), 8.03-7.86 (m, 3H), 7.58-7.49 (m, 3H), 7.36-7.33 (m, 1H), 6.74 (d, 1H, J = 2.2 Hz), 6.53 (d, 1H, J = 2.2 Hz), 6.30 (d, 1H, J = 2.2 Hz), 3.52-3.41 (m, 8H); MS (ESI) 408.1 (M + H)<sup>+</sup>; Purity (HPLC) 100 %.

#### EXAMPLE 149

**N-(7-Piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride**

The title compound was prepared according to the method used for the synthesis of Example 146 (33 %) of a white solid: <sup>1</sup>HNMR (CD<sub>3</sub>OD) δ 7.72-7.69 (m, 3H), 7.57-7.51 (m, 1H), 7.47-7.41 (m, 2H), 6.92 (d, 1H, J = 2.1 Hz), 6.72 (d, 1H, J = 2.1 Hz), 6.58 (d, 1H, J = 2.1), 3.49-3.39 (m, 8H); MS (ESI) 358.1 (M + H)<sup>+</sup>; Purity (HPLC) 96 %.



## EXAMPLE 150

**5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (7-piperazin-1-yl-benzofuran-5-yl)-amide, hydrochloride**

5        The title compound was prepared according to the method used for the synthesis of Example 146 (9 %) of a white solid: <sup>1</sup>HNMR (CD<sub>3</sub>OD) δ 7.74-7.73 (m, 2H), 7.62 (d, 1H, J = 2.2 Hz), 7.38-7.36 (m, 1H), 6.87 (d, 1H, J = 1.8 Hz), 6.64 (d, 1H, J = 2.2 Hz), 6.58 (d, 1H, J = 1.8 Hz), 3.36-3.28 (m, 8H); MS (ESI) 398.2 (M + H)<sup>+</sup>; Purity (HPLC) 98 %.

## 10    EXAMPLE 151

**N-[7-(4-methylpiperazin-1-yl)-1-benzofuran-5-yl]-benzenesulfonamide, hydrochloride**

      The title compound was prepared according to the method used for the synthesis of Example 146 using 1-Methyl-4-(5-Nitro-1-benzofuran-7-yl)piperazine (45 %) of a white solid: <sup>1</sup>HNMR (CD<sub>3</sub>OD) δ 7.74-7.283 (m, 6H), 6.82 (d, 1H, J = 1.8 Hz), 6.62 (d, 1H, J = 2.2 Hz), 6.48 (d, 1H, J = 1.8 Hz), 3.82-2.95 (m, 8H), 2.87 (s, 3H); MS (ESI) 372.1 (M + H)<sup>+</sup>; Purity (HPLC, column X) 96 %.

## EXAMPLE 152

**4-Methyl-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride**

20        4-(5-Amino-benzofuran-7-yl)-piperazine-1-carboxylic acid tert-butyl ester (44 mg, 0.139 mmol) in 3 ml dichloromethane was added to a tube containing p-toluenesulfonyl chloride (32 mg, 0.167 mmol) together with pyridine (100 μl, 1.25 mmol) and left on a shaker over weekend. After purification by preparative HPLC, the resulting Boc-material was treated with HCl in ether and left on a shaker until the salt had formed. The solution was  
25    centrifugated and the supernatant was removed. Ether was added, then centrifugated and decanted (repeated three times) to remove the excess HCl. The remaining ether was finally evaporated in a SpeedVAc concentrator to yield 10 mg of title product. HPLC purity = 94%, m/z = 372.3 (M+H). <sup>1</sup>H NMR (270 MHz, methanol-d<sub>4</sub>) δ ppm 2.35 (s, 3 H) 3.45 (m, 8 H) 6.63 (d, J=1.85 Hz, 1 H) 6.71 (d, J=2.11 Hz, 1 H) 6.88 (d, J=1.85 Hz, 1 H) 7.25 (m, 2 H)  
30    7.58 (m, 2 H) 7.71 (d, J=2.11 Hz, 1 H).

## EXAMPLE 153

**3,4-Dimethoxy-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride**

5 HPLC purity = 92%,  $m/z$  = 418.3 (M+H).  $^1\text{H}$  NMR (270 MHz, methanol- $d_4$ )  $\delta$  ppm  
3.45 (m, 8 H) 3.70 (m, 3 H) 3.81 (m, 3 H) 6.62 (d,  $J$ =1.85 Hz, 1 H) 6.73 (d,  $J$ =2.38 Hz, 1 H)  
6.94 (m, 2 H) 7.17 (d,  $J$ =2.11 Hz, 1 H) 7.29 (dd,  $J$ =8.44, 2.11 Hz, 1 H) 7.72 (d,  $J$ =2.38 Hz, 1 H).

## 10 EXAMPLE 154

**4-Bromo-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride**

HPLC purity = 95%,  $m/z$  = 436.2 (M+H).  $^1\text{H}$  NMR (270 MHz, methanol- $d_4$ )  $\delta$  ppm  
3.46 (m, 8 H) 6.62 (d,  $J$ =1.85 Hz, 1 H) 6.74 (d,  $J$ =2.38 Hz, 1 H) 6.93 (d,  $J$ =1.85 Hz, 1 H)  
7.61 (m, 4 H) 7.73 (d,  $J$ =2.11 Hz, 1 H).

15

## EXAMPLE 155

**2,3-Dichloro-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride**

HPLC purity = 96%,  $m/z$  = 426.2 (M+H).  $^1\text{H}$  NMR (270 MHz, methanol- $d_4$ )  $\delta$  ppm  
3.44 (m, 8 H) 6.67 (d,  $J$ =1.85 Hz, 1 H) 6.72 (d,  $J$ =2.11 Hz, 1 H) 7.01 (d,  $J$ =1.85 Hz, 1 H)  
20 7.34 (t,  $J$ =8.18 Hz, 1 H) 7.70 (m, 2 H) 7.94 (dd,  $J$ =7.92, 1.58 Hz, 1 H).

## EXAMPLE 156

**2,4-Dichloro-5-methyl-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride**

25 HPLC purity = 96%,  $m/z$  = 440.2 (M+H).  $^1\text{H}$  NMR (270 MHz, methanol- $d_4$ )  $\delta$  ppm  
2.30 (s, 3 H) 3.46 (m, 8 H) 6.69 (d,  $J$ =1.85 Hz, 1 H) 6.73 (d,  $J$ =2.11 Hz, 1 H) 7.01 (d,  $J$ =1.85 Hz, 1 H) 7.60 (s, 1 H) 7.71 (d,  $J$ =2.11 Hz, 1 H) 7.87 (s, 1 H).

## EXAMPLE 157

30 **4-Methoxy-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride**

HPLC purity = 93%,  $m/z$  = 388.3 (M+H).  $^1\text{H}$  NMR (270 MHz, methanol- $d_4$ )  $\delta$  ppm  
3.45 (m, 8 H) 3.79 (s, 3 H) 6.72 (d,  $J=2.11$  Hz, 1 H) 6.93 (m, 3 H) 7.63 (m, 3 H) 7.71 (d,  
 $J=2.11$  Hz, 1 H).

5    **EXAMPLE 158**

**4-Chloro-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride**

HPLC purity = 97%,  $m/z$  = 392.3 (M+H).  $^1\text{H}$  NMR (270 MHz, methanol- $d_4$ )  $\delta$  ppm  
3.46 (m, 8 H) 6.63 (d,  $J=1.85$  Hz, 1 H) 6.74 (d,  $J=2.38$  Hz, 1 H) 7.47 (m, 2 H) 7.67 (m, 3 H)  
7.73 (d,  $J=2.11$  Hz, 1 H).

10

**EXAMPLE 159**

**N-(7-Piperazin-1-yl-benzofuran-5-yl)-4-trifluoromethyl-benzenesulfonamide,  
hydrochloride**

HPLC purity = 91%,  $m/z$  = 426.3 (M+H).  $^1\text{H}$  NMR (270 MHz, methanol- $d_4$ )  $\delta$  ppm  
15    3.47 (m, 8 H) 6.64 (d,  $J=1.85$  Hz, 1 H) 6.74 (d,  $J=2.11$  Hz, 1 H) 6.92 (d,  $J=1.85$  Hz, 1 H)  
7.73 (d,  $J=2.11$  Hz, 1 H) 7.84 (m, 4 H).

**EXAMPLE 160**

20    **5-Fluoro-2-methyl-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide,  
hydrochloride**

HPLC purity = 94%,  $m/z$  = 390.3 (M+H).  $^1\text{H}$  NMR (270 MHz, methanol- $d_4$ )  $\delta$  ppm  
2.57 (m, 3 H) 3.46 (m, 8 H) 6.63 (m, 1 H) 6.74 (d,  $J=2.11$  Hz, 1 H) 6.91 (d,  $J=1.85$  Hz, 1 H)  
7.20 (m, 1 H) 7.34 (m, 1 H) 7.56 (dd,  $J=8.71, 2.64$  Hz, 1 H) 7.73 (d,  $J=2.11$  Hz, 1 H).

25    **EXAMPLE 161**

**5-Chloro-thiophene-2-sulfonic acid (7-piperazin-1-yl-benzofuran-5-yl)-amide,  
hydrochloride**

HPLC purity = 94%,  $m/z$  = 398.3 (M+H).  $^1\text{H}$  NMR (270 MHz, methanol- $d_4$ )  $\delta$  ppm  
3.48 (m, 8 H) 6.68 (d,  $J=2.11$  Hz, 1 H) 6.79 (d,  $J=2.38$  Hz, 1 H) 6.97 (d,  $J=3.96$  Hz, 1 H)  
30    7.01 (d,  $J=1.85$  Hz, 1 H) 7.25 (d,  $J=3.96$  Hz, 1 H) 7.76 (d,  $J=2.38$  Hz, 1 H).

## BIOLOGICAL TESTS

The ability of a compound according to the invention to bind a 5-HT<sub>6</sub> receptor, and to be pharmaceutically useful, can be determined using *in vivo* and *in vitro* assays known in the art.

5

*(a) 5-HT<sub>6</sub> Intrinsic Activity Assay*

Antagonists to the 5-HT<sub>6</sub> receptor were characterized by measuring inhibition of 5-HT induced increase in cAMP in HEK 293 cells expressing the human 5-HT<sub>6</sub> receptor (see Boess et al. (1997) *Neuropharmacology* 36: 713-720). Briefly, HEK293/5-HT<sub>6</sub> cells were  
10 seeded in polylysine coated 96-well plates at a density of 25,000 / well and grown in DMEM (Dulbecco's Modified Eagle Medium) (without phenol-red) containing 5% dialyzed Foetal Bovine Serum for 48 h at 37°C in a 5% CO<sub>2</sub> incubator. The medium was then aspirated and replaced by 0.1 ml assay medium (Hanks Balance Salt Solution containing 20 mM HEPES, 1.5 mM isobutylmethylxanthine and 1 mg/ml bovine serum albumin). After addition of test  
15 substances, 50 µl dissolved in assay medium, the cells were incubated for 10 min at 37°C in a 5% CO<sub>2</sub> incubator. The medium was again aspirated and the cAMP content was determined using a radioactive cAMP kit (Amersham Pharmacia Biotech, BIOTRAK RPA559). The potency of antagonists was quantified by determining the concentration that caused 50% inhibition of 5-HT (at [5-HT]= 8 times EC<sub>50</sub>) evoked increase in cAMP, using the formula  
20  $K_i = IC_{50} / (1 + [5HT] / EC_{50})$ .

The compounds in accordance with the invention have a selective affinity to 5-HT<sub>6</sub> receptors with K<sub>i</sub> values between 0.5 nM and 5 µM. The compounds show good selectivity for 5-HT<sub>1a</sub>, 5-HT<sub>2a</sub>, 5-HT<sub>2b</sub>, 5-HT<sub>2c</sub>.

25

*(b) In vivo assay of reduction of food intake*

For a review on serotonin and food intake, see Blundell, J.E. and Halford, J.C.G. (1998) *Serotonin and Appetite Regulation. Implications for the Pharmacological Treatment of Obesity*. *CNS Drugs* 9:473-495.  
30

Obese (ob/ob) mouse is selected as the primary animal model for screening as this mutant mouse consumes high amounts of food resulting in a high signal to noise ratio. To further substantiate and compare efficacy data, the effect of the compounds on food consumption is also studied in wild type (C57BL/6J) mice. The amount of food consumed during 15 hours of infusion of compounds is recorded.

Male mice (obese C57BL/6JBom-Lep<sup>ob</sup> and lean wild-type C57B1/6JBom; Bomholtsgaard, Denmark) 8-9 weeks with an average body weight of 50 g (obese) and 25 g (lean) are used in all the studies. The animals are housed singly in cages at 23±1°C, 40-60 % humidity and have free access to water and standard laboratory chow. The 12/12-h light/dark cycle is set to lights off at 5 p.m. The animals are conditioned for at least one week before start of study.

The test compounds are dissolved in solvents suitable for each specific compound such as cyclodextrin, cyclodextrin/methane sulfonic acid, polyethylene glycol/methane sulfonic acid, saline. Fresh solutions are made for each study. Doses of 30, 50 and 100 mg kg<sup>-1</sup> day<sup>-1</sup> are used. The purity of the test compounds is of analytical grade.

The animals are weighed at the start of the study and randomized based on body weight. Alzet osmotic minipumps (Model 2001D; infusion rate 8 µl/h) are used and loaded essentially as recommended by the Alzet technical information manual (Alza Scientific Products, 1997; Teeuwes and Yam, 1976). Continuous subcutaneous infusion with 24 hours duration is used. The minipumps are either filled with different concentrations of test compounds dissolved in vehicle or with only vehicle solution and maintained in vehicle pre-warmed to 37°C (approx. 1h). The minipumps are implanted subcutaneously in the neck/back region under short acting anesthesia (metofane/enflurane). This surgical procedure lasts approximately 5 min. It takes about 3 h to reach steady state delivery of the compound.

The weight of the food pellets are measured at 5 p.m. and at 8 p. m. for two days before (baseline) and one day after the implantation of the osmotic minipumps. The weighing is performed with a computer assisted Mettler Toledo PR 5002 balance. Occasional spillage

is corrected for. At the end of the study the animals are killed by neck dislocation and trunk blood sampled for later analysis of plasma drug concentrations.

The plasma sample proteins are precipitated with methanol, centrifuged and the supernatant is transferred to HPLC vials and injected into the liquid chromatography /mass spectrometric system. The mass spectrometer is set for electrospray positive ion mode and Multiple Reaction Monitoring (MRM with the transition  $m/z$  316  $\Rightarrow$  221). A linear regression analysis of the standards forced through the origin is used to calculate the concentrations of the unknown samples.

Food consumption for 15 hours is measured for the three consecutive days and the percentage of basal level values is derived for each animal from the day before and after treatment. The values are expressed as mean  $\pm$  SD and  $\pm$  SEM from eight animals per dose group. Statistical evaluation is performed by Kruskal-Wallis one-way ANOVA using the percent basal values. If statistical significance is reached at the level of  $p < 0.05$ , Mann-Whitney U-test for statistical comparison between control and treatment groups is performed.

The compounds according to the invention show an effect in the range of 50-200 mg/kg.

TABLE VI – In vivo efficacy data on the effect of the compounds on Food Intake reduction

EXAMPLES	In vivo efficacy - Food intake (15h) in ob/ob mouse	
	% Inhibition of Food Intake in ob/ob mice at 50 mg/Kg/day, 15h	Free plasma concentration of the compounds at steady state ( $C_{ss,u}$ )
48	23.8	0.008
13	24.1	0.035
53	25.7 <sup>a</sup>	ND
34	51.4	0.078
24	46.2	0.0076

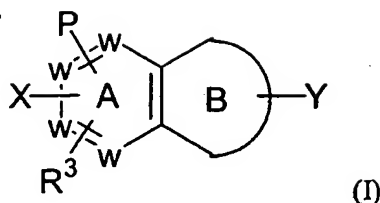
19	69.6	0.150
27	68.9	0.008
30	60.1	0.275
29	71	0.33
14	41 <sup>b</sup>	0.23

<sup>a</sup> The effect on Food Intake reported in the table was obtained at the dose of 14.8 mg/kg/d

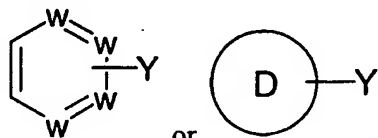
<sup>b</sup> The effect on Food Intake reported in the table was obtained at the dose of 100 mg/kg/d

## WHAT IS CLAIMED IS:

1. A compound of the formula I



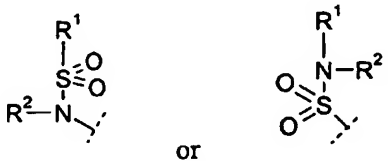
or a pharmaceutically acceptable salt thereof, wherein:



ring B is ; in which D is a five-membered heterocyclic or heteroaryl ring, said ring comprising one or two atoms selected from the group consisting of nitrogen, sulfur and oxygen, with the proviso that when D contains an oxygen atom, D is heteroaryl;

W is N or  $-(CH)-$ , provided that not more than three groups W are N in both rings A and B together;

P is



P and  $R^3$  are bound to the same ring and are disposed in meta- or para-positions relative to each other;

$R^1$  is

(a)  $C_{1-6}$  alkyl,



- (b) C<sub>1-6</sub> alkoxyalkyl,
- (c) straight or branched C<sub>1-6</sub> hydroxyalkyl,
- (d) straight or branched C<sub>1-6</sub> alkylhalides; or
- (e) a group Ar;

5

Ar is

- (a) phenyl,
- (b) 1-naphthyl,
- (c) 2-naphthyl,
- 10 (d) benzyl,
- (e) cinnamoyl,
- (f) a 5 to 7-membered, optionally aromatic, partially saturated or completely saturated, heterocyclic ring containing 1 to 4 heteroatoms, selected from oxygen, nitrogen and sulfur, or
- (g) a bicyclic ring system comprising at least one heterocyclic ring according to (f).

15

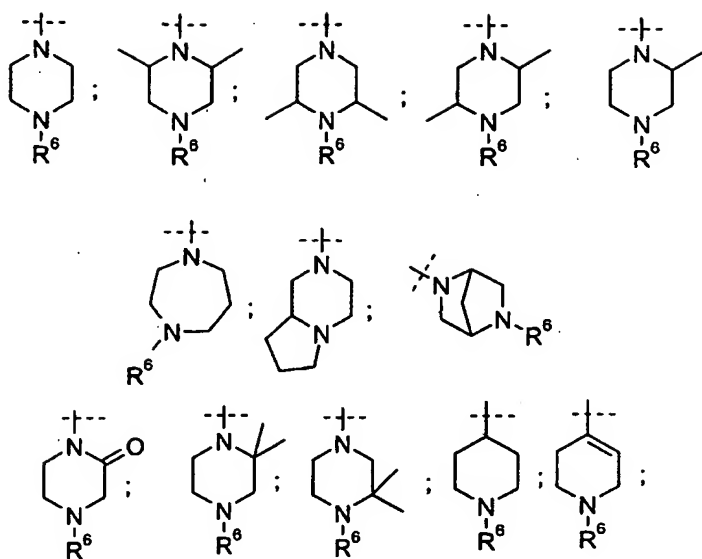
wherein the group Ar is substituted in one or more positions with

- (a) H, X or Y, or
- (b) a 5 to 7-membered, optionally aromatic, partially saturated or completely saturated, heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or
- 20 sulfur;

R<sup>2</sup> is

- (a) H,
  - (b) C<sub>1-6</sub> alkyl,
  - 25 (c) C<sub>1-6</sub> alkoxy,
  - (d) straight or branched C<sub>1-6</sub> hydroxyalkyl, or
  - (e) straight or branched C<sub>1-6</sub> alkylhalides;
- or R<sup>1</sup> and R<sup>2</sup> are linked to form a group (CH<sub>2</sub>)<sub>4</sub>O;

One of R<sup>3</sup> is a group



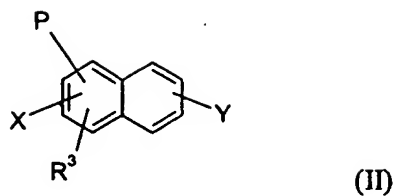
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X and Y are independently

- (a) H,
- (b) halogen,
- (c) C<sub>1-6</sub> alkyl,
- 10 (d) -CF<sub>3</sub>,
- (e) hydroxy,
- (f) C<sub>1-6</sub> alkoxy,
- (g) C<sub>1-4</sub> alkenyl;
- (h) phenyl;
- 15 (i) phenoxy,
- (j) benzyloxy,
- (k) benzoyl,
- (l) -OCF<sub>3</sub>,
- (m) -CN,
- 20 (n) straight or branched C<sub>1-6</sub> hydroxyalkyl,

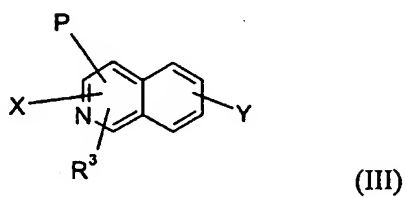
- (o) straight or branched C<sub>1-6</sub> alkylhalides,
- (p) -NH<sub>2</sub>,
- (q) -NHR<sup>4</sup>,
- (r) -NR<sup>4</sup>R<sup>5</sup>,
- 5 (s) -NO<sub>2</sub>,
- (t) -CONR<sup>4</sup>R<sup>5</sup>,
- (u) -NHSO<sub>2</sub>R<sup>4</sup>,
- (v) -NR<sup>4</sup>COR<sup>5</sup>,
- (x) -SO<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>,
- 10 (z) -C(=O)R<sup>4</sup>,
- (aa) -CO<sub>2</sub>R<sup>4</sup>, or
- (ab) -S(O)<sub>n</sub>R<sup>4</sup>; wherein n is 0, 1, 2 or 3;
- (ac) -S-(C<sub>1-6</sub>)alkyl
- (ad) -SCF<sub>3</sub>
- 15 R<sup>4</sup> and R<sup>5</sup> are independently
  - (a) H,
  - (b) C<sub>1-6</sub> alkyl,
  - (c) C<sub>3-7</sub> cycloalkyl, or
  - 20 (d) Ar, as defined above for R<sup>1</sup>;
 alternatively, R<sup>4</sup> and R<sup>5</sup> are linked to form a group (CH<sub>2</sub>)<sub>2</sub>O, (CH<sub>2</sub>)<sub>4</sub>O or (CH<sub>2</sub>)<sub>3-5</sub>; and
   
 R<sup>6</sup> is
  - (a) H, or
  - 25 (b) straight or branched C<sub>1-6</sub> alkyl.

2. The compound according to claim 1 of the general formula II



wherein R<sup>3</sup>, P, X and Y are as defined for formula (I).

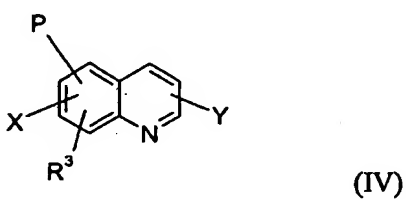
- 5 3. The compound according to claim 1 of the general formula III



wherein R<sup>3</sup>, P, X and Y are as defined for formula (I).

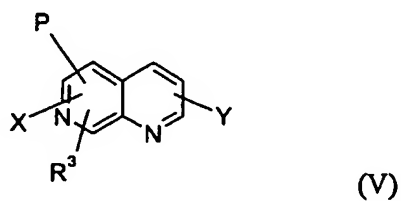
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4. The compound according to claim 1 of the general formula IV



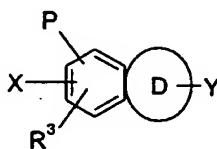
15 wherein R<sup>3</sup>, P, X and Y are as defined for formula (I).

5. The compound according to claim 1 of the general formula V



wherein  $R^3$ , P, X and Y are as defined for formula (I).

6. The compound according to claim 1 of the general formula VI



(VI)

wherein  $R^3$ , P, X and Y are as defined for formula (I); and wherein D is a five-membered heterocyclic or heteroaryl ring, said ring comprising one or two atoms selected from the group consisting of nitrogen, sulfur and oxygen, with the proviso that when D contains an oxygen atom, D is heteroaryl. When the heteroaryl ring comprises one or two nitrogen atoms, a group  $R^6$  is attached at the secondary nitrogen.

7. The compound according to claim 1, wherein

$R^1$  is

- (a)  $C_{1-6}$  alkyl, or
- (e) a group Ar;

Ar is

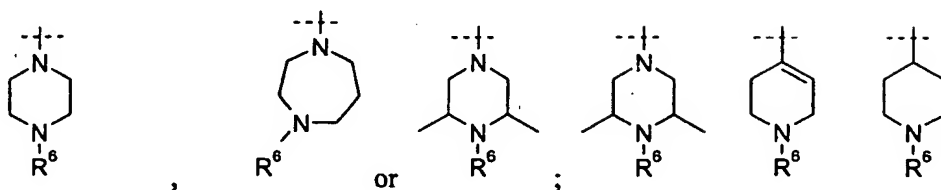
- (a) phenyl,
- (b) 1-naphthyl,
- (c) 2-naphthyl, or
- (f) a 5 to 7-membered, optionally aromatic, partially saturated or completely saturated, heterocyclic ring containing 1 to 4 heteroatoms, selected from oxygen, nitrogen and sulfur;

wherein the group Ar is substituted in one or more positions with X or Y; wherein X or Y is

- (a) H,  
 (b) halogen,  
 (c) C<sub>1-6</sub> alkyl,  
 (d) -CF<sub>3</sub>,  
 5 (f) C<sub>1-6</sub> alkoxy,  
 (g) C<sub>1-4</sub> alkenyl;  
 (l) -OCF<sub>3</sub>, or  
 (n) straight or branched C<sub>1-6</sub> hydroxyalkyl.

- 10 R<sup>2</sup> is  
 (a) H, or  
 (b) C<sub>1-3</sub> alkyl, in particular methyl;  
 or R<sup>1</sup> and R<sup>2</sup> are linked to form a group (CH<sub>2</sub>)<sub>4</sub>O;

- 15 R<sup>3</sup> is



wherein R<sup>6</sup> is

- (a) H, or  
 20 (b) C<sub>1-6</sub> alkyl, in particular methyl;

X and Y are H; and/or

D is pyrrolyl, thienyl or furanyl.

25

8. The compound according to claim 2 or 7, which is the compound  
 N-(4-Methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride  
 N-(2,4-Dimethoxyphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride

- N-(3,4-di-Fluorophenyl)-4-(4-methyl-1,4-diazepan-1-yl)-1-naphthalenesulfonamide,  
hydrochloride
- N-(3-Fluorophenyl)-4-(4-methyl-1,4-diazepan-1-yl)-1-naphthalenesulfonamide,  
hydrochloride
- 5 4-(4-Ethyl-1-piperazinyl)-N-phenyl-1-naphthalenesulfonamide, hydrochloride
- 4-Hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl-N-(4-methylphenyl)-1-naphthalenesulfonamide,  
hydrochloride
- N-(3,4-Dimethoxyphenyl)-4-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl-1-  
naphthalenesulfonamide, hydrochloride
- 10 4-(4-Ethyl-1-piperazinyl)-N-(4-methylphenyl)-1-naphthalenesulfonamide, hydrochloride
- N-(3,4-Dimethoxyphenyl)-4-(3-methyl-1-piperazinyl)-1-naphthalenesulfonamide,  
hydrochloride
- N-(4-Methylphenyl)-4-(4-methyl-1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride
- N-[4-(2,5-Diazabicyclo[2.2.1]hept-2-yl)-1-naphthyl]-4-methylbenzenesulfonamide,  
15 hydrochloride
- N-(4-Methylphenyl)-4-(3-methyl-1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride
- N-(2-Naphthyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride
- N-Methyl-N-(4-methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride
- 4-(1,4-Diazepan-1-yl)-N-(4-methylphenyl)-1-naphthalenesulfonamide, hydrochloride
- 20 4-(1,4-Diazepan-1-yl)-N-(2-methoxy-4-methylphenyl)-1-naphthalenesulfonamide,  
hydrochloride
- N-(2-Methoxy-4-methylphenyl)-4-(3,5-trimethyl-1-piperazinyl)-1-naphthalenesulfonamide,  
hydrochloride
- 4-(4-Isopropyl-1-piperazinyl)-N-(4-methylphenyl)-1-naphthalenesulfonamide, hydrochloride
- 25 4-Bromo-N-(4-piperazin-1-yl)-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 2,5-di-Chloro-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride
- 2-Chloro-4-fluoro-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride
- 2,3-di-Chloro-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride
- 2,4-di-Chloro-5-methyl-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride
- 30 3-tri-Fluoromethyl-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride
- 2-tri-Fluoromethyl-N-[4-(1-piperazinyl)-1-naphthyl]benzenesulfonamide, hydrochloride

- 4-Bromo-N-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide,  
hydrochloride
- Naphthalene-1-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride
- Naphthalene-1-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride
- 5 2,5-Dichloro-thiophene-3-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide,  
hydrochloride
- 4-Methoxy-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 4-Chloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 2-Chloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 10 N-(4-Piperazin-1-yl-naphthalen-1-yl)-4-trifluoromethyl-benzenesulfonamide, hydrochloride
- 4-Fluoro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 5-Fluoro-2-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 4-Phenoxy-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 2-Bromo-4-iodo-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 15 Thiophene-2-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride
- 5-Chloro-thiophene-2-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide, hydrochloride
- 3-Methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 4-Butyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide hydrochloride
- 2,4,6-Trimethyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide hydrochloride
- 20 2,4,5-Trichloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 4-Iodo-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 2-Methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 3,4-Dichloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 5-Bromo-2-methoxy-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide,  
25 hydrochloride
- 2-Bromo-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 3-Chloro-2-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 2,6-Dichloro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 3-Methoxy-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 30 3-Chloro-4-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 4-Bromo-2-fluoro-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride



- 2,4-Dichloro-6-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide,  
hydrochloride
- 4-Bromo-2-methyl-N-(4-piperazin-1-yl-naphthalen-1-yl)-benzenesulfonamide, hydrochloride
- 4,5-Dichloro-thiophene-2-sulfonic acid (4-piperazin-1-yl-naphthalen-1-yl)-amide,  
5 hydrochloride
- N-Methyl-N-(4-bromo-2-methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide,  
hydrochloride
- N-Methyl-N-(5-fluoro-2-methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide,  
hydrochloride
- 10 N-Methyl-N-(2-methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride
- N-Methyl-N-(3-chloro-2-methylphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide,  
hydrochloride
- 2,5-di-Chlorothiophen-3-yl-N-Methyl-N-(2,5-dichlorothiophen-3-yl)-4-(1-piperazinyl)-1-  
naphthalenesulfonamide, hydrochloride
- 15 N-Methyl-N-(2-naphthyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride
- N-Methyl-N-(1-naphthyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride
- N-Methyl-N-(4-chlorophenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride
- N-Methyl-N-(4-methoxyphenyl)-4-(1-piperazinyl)-1-naphthalenesulfonamide, hydrochloride
- 5-Fluoro-2-methyl-N-{4-[(2R,5S)-2,5-dimethyl-1-]piperazin-1-yl-1-  
20 naphthyl}benzenesulfonamide, hydrochloride
- 5-Fluoro-2-methyl-N-[4-(1,2,3,6-tetrahydropyridin-4-yl)-1-naphthyl]benzenesulfonamide,  
hydrochloride
- N-[4-(4-Methyl-1-piperazinyl)-2-naphthyl]benzenesulfonamide, hydrochloride
- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid phenylamide, hydrochloride
- 25 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-methoxy-phenyl)-amide, hydrochloride
- 4-(*cis*-3,5-Dimethyl-piperazin-1-yl)-naphthalene-1-sulfonic acid (2-methoxy-phenyl)-amide,  
hydrochloride
- 4-(*cis*-3,5-Dimethyl-piperazin-1-yl)-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide,  
hydrochloride
- 30 4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide, hydrochloride
- 4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid phenylamide, hydrochloride

- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-chloro-phenyl)-amide, hydrochloride
- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-methylsulfanyl-phenyl)-amide,  
hydrochloride
- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid methyl-naphthalen-1-yl-amide, hydrochloride
- 5 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2,3-dihydro-benzo[1,4]dioxin-6-yl)-methyl-  
amide, hydrochloride
- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2,3-dihydro-benzo[1,4]dioxin-6-yl)-amide,  
hydrochloride
- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid methyl-(2-methylsulfanyl-phenyl)-amide,  
10 hydrochloride
- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid methyl-(3-trifluoromethyl-phenyl)-amide,  
hydrochloride
- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-chloro-4-methyl-phenyl)-methyl-amide,  
hydrochloride
- 15 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-ethyl-phenyl)-methyl-amide, hydrochloride
- 4-(3,5-Dimethyl-piperazin-1-yl)-naphthalene-1-sulfonic acid (2-isopropyl-phenyl)-amide,  
hydrochloride
- 4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (2-isopropyl-phenyl)-amide, hydrochloride
- 4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-ethyl-phenyl)-amide, hydrochloride
- 20 N-(2-Fluorophenyl)-4-piperazin-1-yl-naphthalene-1-sulfonamide, hydrochloride
- 4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-trifluoromethyl-phenyl)-amide,  
hydrochloride
- N-(2,4-di-Fluorophenyl)-4-piperazin-1-yl-naphthalene-1-sulfonamide, hydrochloride
- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-trifluoromethoxy-phenyl)-amide,  
25 hydrochloride
- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-3-phenoxyphenyl)-amide, hydrochloride
- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-trifluoromethoxy-phenyl)-amide,  
hydrochloride
- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-chloro-5-methyl-phenyl)-amide,  
30 hydrochloride

- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-trifluoromethoxy-phenyl)-amide,  
hydrochloride
- 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2-chloro-5-methyl-phenyl)-amide,  
hydrochloride
- 5 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (4-isopropyl-phenyl)-amide, hydrochloride  
N-(3,5-di-Fluorophenyl)-4-piperazin-1-ynaphthalene-1-sulfonamide, hydrochloride  
1-[4-(3,4-Dihydroquinolin-1(2H)-ylsulfonyl)-1-naphthyl]piperazine, hydrochloride  
4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-nitro-phenyl)-amide, hydrochloride  
4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-nitro-phenyl)-amide, hydrochloride
- 10 4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (3-nitro-phenyl)-methyl-amide,  
hydrochloride  
N-(4-Methylphenyl)-4-piperazin-1-ynaphthalene-1-sulfonamide, hydrochloride  
N-(3-Chloro-4-methylphenyl)-4-piperazin-1-ynaphthalene-1-sulfonamide, hydrochloride  
4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (2,3-dimethyl-phenyl)-methyl-amide,  
15 hydrochloride  
4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (4-isopropyl-phenyl)-amide, hydrochloride  
4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (4-isopropyl-phenyl)-methyl-amide,  
hydrochloride  
4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (2,4-dimethyl-phenyl)-amide,  
20 hydrochloride  
4-[1,4]Diazepan-1-yl-naphthalene-1-sulfonic acid (2-chloro-5-methyl-phenyl)-amide,  
hydrochloride  
4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2,5-dimethoxy-phenyl)-amide, hydrochloride  
4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-acetyl-phenyl)-amide, hydrochloride
- 25 4-Piperazin-1-yl-naphthalene-1-sulfonic acid (2,4-dimethyl-phenyl)-amide, hydrochloride  
4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-trifluoromethyl-phenyl)-amide,  
hydrochloride  
4-Piperazin-1-yl-naphthalene-1-sulfonic acid biphenyl-2-ylamide, hydrochloride  
4-Piperazin-1-yl-naphthalene-1-sulfonic acid (3-benzyloxy-phenyl)-amide, hydrochloride
- 30 N-(4-fluorophenyl)-4-piperazin-1-ynaphthalene-1-sulfonamide, hydrochloride  
N-(3-Ethylphenyl)-4-piperazin-1-ynaphthalene-1-sulfonamine, hydrochloride

4-Piperazinyl-N-[3-(trifluoromethyl)phenyl]naphthalene-1-sulfonamide, hydrochloride  
4-Piperazinyl-N-[3-benzoylphenyl]naphthalene-1-sulfonamide, hydrochloride  
4-Piperazinyl-N-[3-(4-bromo-1-methyl-1H-pyrazol-3-yl)phenyl]naphthalene-1-sulfonamide,  
hydrochloride  
5 4-Piperazinyl-N-[3-biphenylphenyl]naphthalene-1-sulfonamide, hydrochloride

9. The compound according to claim 3 or 7, which is the compound

N-[1-(4-Methyl-1-piperazinyl)-3-isoquinoliny]benzenesulfonamide, hydrochloride

2,4-di-Fluoro-N-[1-(4-methyl-1-piperazinyl)-3-isoquinoliny]benzenesulfonamide,

10 hydrochloride

4-Bromo-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide,  
hydrochloride

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [1-(4-methyl-piperazin-1-yl)-  
isoquinolin-3-yl]-amide, hydrochloride

15 3-Chloro-2-methyl-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide,  
hydrochloride

3,4-Dichloro-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide,  
hydrochloride

4-Methyl-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide,  
20 hydrochloride

3-Methoxy-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide,  
hydrochloride

5-Chloro-thiophene-2-sulfonic acid [1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-amide,  
hydrochloride

25 N-{2-Chloro-4-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-ylsulfamoyl]-phenyl}-acetamide  
hydrochloride

2,5-Dichloro-thiophene-3-sulfonic acid [1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-  
amide, hydrochloride

N-[1-(4-Methyl-piperazin-1-yl)-isoquinolin-3-yl]-3-trifluoromethyl-benzenesulfonamide,  
30 hydrochloride

N-[1-(4-Methyl-piperazin-1-yl)-isoquinolin-3-yl]-4-phenoxy-benzenesulfonamide,  
hydrochloride

5-Bromo-2-methoxy-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide,  
hydrochloride

5 2-Methanesulfonyl-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide,  
hydrochloride

3,5-Dimethyl-isoxazole-4-sulfonic acid [1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-  
amide, hydrochloride

2,4,6-Trimethyl-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide,  
10 hydrochloride

3,4-Dimethoxy-N-[1-(4-methyl-piperazin-1-yl)-isoquinolin-3-yl]-benzenesulfonamide,  
hydrochloride

10. The compound according to claim 4 or 7, which is the compound

15 N-(8-{[2-(di-Methylamino)ethyl]amino}-5-quinolinyl)benzenesulfonamide, hydrochloride

11. The compound according to claim 5 or 7, which is the compound

4-Methyl-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic acid

4-Bromo-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic acid

20 N-(8-Piperazin-1-yl-1,7-naphthyridin-6-yl)naphthalene-1-sulfonamide, trifluoroacetic acid

N-(8-Piperazin-1-yl-1,7-naphthyridin-6-yl)butane-1-sulfonamide, trifluoroacetic acid

3-Trifluoromethyl-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide,  
trifluoroacetic acid

3,4-Dimethoxy-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide,  
25 trifluoroacetic acid

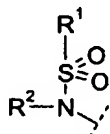
2,4-Dichloro-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)benzenesulfonamide, trifluoroacetic  
acid

N-(8-Piperazin-1-yl-1,7-naphthyridin-6-yl)thiophene-2-sulfonamide, trifluoroacetic acid

1-Phenyl-N-(8-piperazin-1-yl-1,7-naphthyridin-6-yl)methanesulfonamide, trifluoroacetic  
30 acid

12. The compound according to claim 6 or 7, which is the compound  
 3-Cyanophenyl-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride  
 4-Phenoxy-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride  
 1-Naphthyl-N-(7-piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride  
 5 N-(7-Piperazin-1-yl-benzofuran-5-yl)-benzenesulfonamide, hydrochloride  
 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (7-piperazin-1-yl-benzofuran-5-yl)-  
 amide, hydrochloride  
 N-[7-(4-Methylpiperazin-1-yl)-1-benzofuran-5-yl]-benzenesulfonamide, hydrochloride

- 10 13. A process for the preparation of a compound according to any one of claims 1 to 7

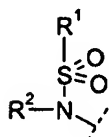


wherein P is , said method comprising the steps of:

- (a) nucleophilic aromatic substitution of the aromatic halogen atom in 1-chloro-3-nitronaphthalene or 1-chloro-4-nitronaphthalene with aliphatic or aromatic diamines;  
 (b) reduction of the nitro group in 1-diamine-3-nitronaphthalene or 1-diamine-4-nitronaphthalene obtained in step (a) to form 1-diamine-3-NH<sub>2</sub>-naphthalene or 1-diamine-4-NH<sub>2</sub>-naphthalene, respectively; and  
 15 (c) synthesis of a sulfonamide by reacting 1-diamine-3-NH<sub>2</sub>-naphthalene or 1-diamine-4-NH<sub>2</sub>-naphthalene obtained in step (b) with a suitable sulfonyl chloride.

- 20 14. The process of claim 13, wherein step (a) is by means of Palladium catalyzed nucleophilic substitution.

15. A process for the preparation of a compound according to claim 1, wherein P is



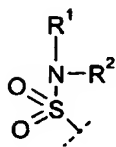
, said method comprising the steps of:

- 25 (a) nucleophilic aromatic substitution of the trifluoromethanesulfonate group in 2-trifluoromethanesulfonate-5-nitroquinoline with aliphatic or aromatic diamines;

- (b) reduction of the nitro group in 2-diamine-5-nitroquinoline obtained in step (a) to form 2-diamine-5-NH<sub>2</sub>-quinoline; and
- (c) synthesis of a sulfonamide by reacting 2-diamine-5-NH<sub>2</sub>-quinoline obtained in step (b) with a suitable sulfonyl chloride.

5

16. A process for the preparation of a compound according to claim 1, wherein P is



, said method comprising the steps of:

- (a) reacting a fluoronaphthalene and chlorosulfonic acid under acidic conditions, to introduce a sulfonyl chloride group in the para position to the carbon having the fluoro atom;
- (b) reacting the product of step (a) with an aliphatic or aromatic primary amine to give a sulfonamide; and
- (c) reaction of the product of step (b) with a diamine.

10

15 17. A pharmaceutical formulation containing a compound according to claim 1 as active ingredient, in combination with a pharmaceutically acceptable diluent or carrier.

18. A method for the treatment or prophylaxis of obesity, type II diabetes, and/or disorders of the central nervous system, which comprises administering to a mammal in need of such treatment an effective amount of a compound according to claim 1.

20

19. A method for reducing body-weight, comprising administering to a subject in need thereof an effective amount of a compound of claim 1.

25 20. A method for modulating 5-HT<sub>6</sub> receptor activity, comprising administering to a subject in need thereof an effective amount of a compound of claim 1.

21. A compound according to claim 1 for use in therapy.

22. A compound according claim1 for use in the treatment or prophylaxis of obesity, type II diabetes, and/or disorders of the central nervous system.
- 5 23. Use of a compound according to claim 1 for the manufacture of a medicament for use in the treatment or prophylaxis of obesity, type II diabetes, and/or disorders of the central nervous system.
- 10 24. A pharmaceutical formulation for use in the treatment or prophylaxis of obesity, type II diabetes, and/or disorders of the central nervous system wherein the active ingredient is a compound according to claim1.



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01126

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC7: C07C 311/21, C07D 295/04, C07D 487/06, C07D 241/04, C07D 215/38, C07D 217/22, C07D 403/04, C07D 405/04 // A61K 31/18, 31/47, 31/495, 31/496, According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC7: C07C, C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
EPO-INTERNAL, CHEM. ABS DATA		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0132646 A2 (SMITHKLINE BEECHAM P.L.C.), 10 May 2001 (10.05.01) --	1-24
X	WO 9827081 A1 (SMITHKLINE BEECHAM PLC), 25 June 1998 (25.06.98) --	1-24
X	WO 9902502 A2 (SMITHKLINE BEECHAM PLC), 21 January 1999 (21.01.99) --	1-24
X	EP 1020445 A1 (EISAI CO., LTD.), 19 July 2000 (19.07.00), see compound 422 --	1,3,13-17, 21-22,24
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
12 Sept 2002		17 -09- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer  Eva Johansson/Eö Telephone No. +46 8 782 25 00

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01126

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9942465 A2 (SMITHKLINE BEECHAM PLC), 26 August 1999 (26.08.99) --	1-24
A	WO 9937623 A2 (SMITHKLINE BEECHAM PLC), 29 July 1999 (29.07.99) --	1-24
A	EP 0815861 A1 (F. HOFFMANN-LA ROCHE AG), 7 January 1998 (07.01.98) --	1-24
A	EP 0701819 A2 (PFIZER INC.), 20 March 1996 (20.03.96) -- -----	1-24

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE02/01126

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **18-20**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see next sheet**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE02/01126

Claims 18-20 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

06/07/02

International application No.

PCT/SE 02/01126

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